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ERYTHROBLASTOSIS FETALIS. VII. TREATMENT WITH EXCHANGE TRANSFUSION*

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BOSTON

EXCHANGE transfusion has become a rather widely used procedure in the treatment of erythroblastosis fetalis, though it has by no means achieved universal acceptance. A number of technics have been described.[1-3] Recent studies[4, 5] have clearly demonstrated the value of this procedure in the treatment of erythroblastotic infants, particularly in the prevention of kernicterus. The purpose of this paper is to describe the technic of exchange transfusion, as performed at the Infants' and Children's hospitals, Children's Medical Center, and the Boston Lying-in Hospital, to outline the indications for its use and to present the results of its use in more than 350 erythroblastotic babies.

Exchange transfusion of the newborn infant is not to be undertaken lightly, since there are a number of hazards to be avoided. It is sufficiently easy, however, that the physician who is experienced in the management of newborn infants can undertake the technical procedure with confidence after a moderate amount of practice. The technic described below is probably the simplest of the methods in common use, as well as the least traumatic to the baby. The procedure as originally adopted in this clinic has undergone a number of modifications, both in equipment and in details of technic. Use of the technic as presented here will help the physician to avoid most of the difficulties that we have had in the past.

EQUIPMENT

The demonstration by Ingraham and his coworkers[6] that polyethylene tubing could be used safely, and without the nuisance of blood clotting within the tube, led to the initial trials of this material in the umbilical vein of newborn erythroblastotic babies at the Boston Lying-in Hospital by one of us (W.O.T.) in November, 1946. The technic involves alternate withdrawal and replacement of blood through a single polyethylene tube, which has a definite mechanical advantage over methods using two separate blood vessels. The umbilical vein is the largest accessible vein and is readily identified in the cut end of the umbilical cord, and its use leaves no scars. To minimize the chilling effect of the exchange transfusion, the baby is kept in a covered, warmed incubator throughout the procedure except for the few minutes required for physical examination, application of simple restraints and antiseptic preparation of the cord and the skin of the abdomen. Technical failures have been rare since the method became standardized.

Table 1 lists the important items of equipment that have survived the test of time. Figure 1 shows the instruments included in the sterile pack.

TABLE 1. *Equipment Used in the Performance of Exchange Transfusion.*

STERILE PACK	
Metal tray	Scissors
Umbilical-vein cannula*	2 monel-metal basins§
Tuohy adapter†	Needles¶
2 3-way stopcocks‡	Specimen tubes‖
2 20-cc. Luer-Lok syringes	6 hand towels
1 10-cc. syringe	2 half sheets
Rubber tubing	2 towel clips
Transfusion set, recipient	Gauze sponges
Mosquito snaps	Umbilical-cord tape
Toothed forceps	Blunt probe
15-cm. stainless steel rule	

UNSTERILE EQUIPMENT	
Hess bed	Oxygen
Diapers	Gravity pole
Suction pump	Waste bucket

Monel-metal canister, filled with 1:1000 aqueous Zephiran,** containing 38-cm. lengths of polyethylene tubing††

*Becton-Dickinson Co.
†C. F. Bard Co.
‡Becton-Dickinson Co., Cat. No. LL/S
§10 cm. in diameter
¶18, 19, 20, and 24 gauge
‖Oxalate, and plain
**Benzalkonium chloride, *U.S.P.*
††Clay Adams Co., Cat. No. A 2590 and 2591

*From the Departments of Pediatrics and Obstetrics, Harvard Medical School, the Children's Medical Center and the Boston Lying-in Hospital. This work was aided by grants from the United States Public Health Service.

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Notes on Equipment

Hess Bed

The Hess bed (Fig. 2) is a convenient receptacle for the baby because of its flat and rigid top (which can be used as an instrument table). Most other incubators have a hinged top that must be raised for one to gain access to the baby. A piece of plywood that will fit securely over the foot end of an ordinary open incubator serves admirably as a place for laying instruments and so forth and from which the sterile drapes will not be disturbed by the baby's kicking. A wire similar to that used by

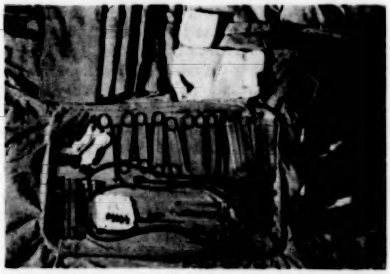


Figure 1. *Materials Included in Sterile Pack for Exchange Transfusion.*

The metal tray protects the instruments from contamination when the cloth wrappings become wet. The spherical object at the end of the long rubber tube is a metal sinker (Becton-Dickinson No. 330 S), which prevents the end of the tubing from gyrating when blood is ejected through it. This set contains an extra pair of stopcocks.

anesthetists or other device should be added for supporting the sterile drapes above and in front of the baby's face. The Hess bed with its two openings serves very well, since it provides separate openings, conveniently spaced, for operator and nurse, and allows for easy sterile draping.

Restraints

In restraining the baby, diapers folded into long, narrow strips can be wrapped around each arm and leg and tucked under the mattress (Fig. 3). Such an arrangement, although not confining the baby too rigidly, keeps him sufficiently quiet.

Suction

Automatic suction (pump) is superior to mouth suction (bulb and catheter) because of the relative inaccessibility of the baby after the sterile drapes are applied. Many babies have required frequent suction. Oxygen is given continuously during the procedure.

Umbilical-Vein Catheter

The umbilical-vein cannula (Fig. 4 and 5) is designed to provide, in conjunction with the polyethylene tubing, an *airtight* apparatus that can be more easily inserted into the umbilical vein than the naked plastic tubing, allows a tight tie to be placed around the umbilical cord after insertion of the tubing and serves as a landmark once the tubing is in place. The details of its construction are shown in Figure 4.

Tuohy Adapter

The Tuohy adapter has a small internal caliber that does not allow passage of the plastic tubing.

Figure 2. *The Hess Bed Used for Exchange Transfusion. This model has two square holes in the top with covers, both of which are hinged at the head end, which is the most convenient arrangement.*

A 49-gauge drill has been found to be the correct size for enlarging the internal caliber of the Tuohy adapter so that the polyethylene tubing will go through easily. Screwing down on the knurled end compresses a rubber bushing, which gently grips the plastic tubing and provides an airtight immobile connection. Both the Tuohy adapter and the umbilical-vein cannula should be kept in the unscrewed position when not in use, to avoid permanent distortion of the rubber gaskets.

Polyethylene Tubing

The polyethylene tubing is prepared for use by mechanical cleaning with running water (as for rubber tubing for intravenous equipment) and then soaked for at least eighteen hours in 1:1000 aqueous

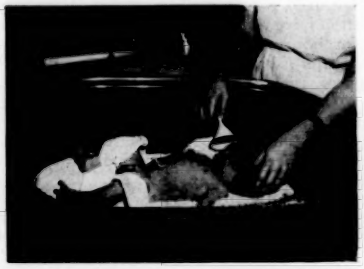


FIGURE 3. *Restraining the Baby.*
Folded diapers around each arm and leg are tucked under the mattress.

solution of Zephiran. The inside of the tubing should be filled with the Zephiran solution during the required eighteen hours of sterilization. Tubing so prepared may be kept indefinitely in a covered

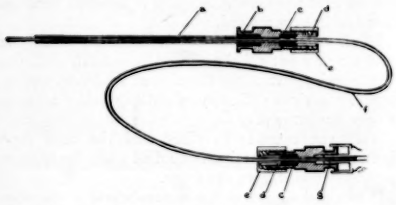


FIGURE 4. *Details of Construction of the Umbilical-Vein Cannula and the Tuohy Adapter (the Former Is in the Upper Part of This Cut-Away Drawing, and the Latter in the Lower).*
a = *13 gauge steel tubing, soldered* (b) *into female Luer end of Tuohy adapter.*
c = *Rubber gasket (acutally a short piece of ordinary No. 8 rubber catheter).*
d = *Metal bushing, which compresses rubber gasket when threaded end* (e) *is screwed in, making an airtight seal at point* (c).
f = *"18-gauge" polyethylene tubing.*
g = *Male end of stopcock (Becton-Dickinson LL/S), showing end of polyethylene tubing lying within its lumen.*

monel-metal canister sealed with adhesive tape. The plastic tubing can be used over and over again, and is most conveniently cleaned, rinsed and replaced in the canister of Zephiran solution directly after its use and while the operator still has on his sterile gown and gloves.

ASSEMBLING THE APPARATUS

When the operator is scrubbed and gowned, the sterile pack is opened, and about 200 cc. of sterile saline solution is poured into each of the monel-metal basins, and approximately 1 cc. of heparin solution (1:100) is added. The polyethylene tubing is removed from its canister of Zephiran solution with sterile forceps, rinsed inside and out with saline solution with the aid of a syringe and 18-gauge needle and inspected to make certain that both ends

FIGURE 5. *Detail of Assembly of Apparatus.*
The polyethylene tubing protrudes about 0.3 cm. at each end. The Tuohy adapter can now be connected to the end of the stopcock.

are cut off square and smooth. A 38-cm. length is inserted through the umbilical vein cannula and fixed in position by *just sufficient* tightening of the threaded end. It is allowed to protrude about 0.3 cm. beyond the end of the cannula (Fig. 5), far enough so that the leading point of the apparatus is the relatively soft and pliable plastic, but not so far as to lose the rigidity provided by the metal cannula. The other end of the polyethylene tubing is inserted through the Tuohy adapter, and fixed in position with about 0.3 cm. protruding beyond the female luer end of the adapter. The two three-way stopcocks are then fastened in tandem and attached to the Tuohy adapter. The proximal end of the plastic tubing is now protruding for a short distance into the lumen of the distal stopcock, an arrangement that practically eliminates clotting of blood in the apparatus. The so-called "18-gauge" tubing* is ordinarily used. A short length of fairly thick-walled rubber tubing is attached to the sidearm of the distal stopcock to receive the end of the sterile recipient set. A longer length of thin-walled rubber

*Clay Adams Company, Cat. No. A2590.

tubing (4 ft. is usually a convenient length) is attached to the sidearm of the proximal stopcock for an exhaust tube.

Preparation of the Baby

After suction of the pharynx, if necessary, and immobilization of the baby, the abdomen and umbilical cord are prepared as for a laparotomy. Colored tincture of Zephiran has been used with satisfactory results. The top is then put in place on the Hess bed, with both hatches open, and the top of the Hess bed, as well as the baby's abdomen, is aseptically draped with towels and half sheets. The drapes can be tucked down into the hole as they are being placed, which helps anchor them in position. A length of umbilical-cord tape is passed around the cord just distal to the skin margin, and tied loosely with a single half-hitch knot. The apparatus is placed on the sterile drapes, with the long tube hanging over the side into a bucket, and the sterile recipient set is connected up with the donor blood. After clearing the tubing of the recipient set of air, and connecting it to the transfusion apparatus, the plastic tubing is cleared of air bubbles (using saline solution) and the proximal stopcock is turned so as to connect the syringe with the discharge tube. (This position of the proximal stopcock makes the system a closed one, and should be used whenever the syringe is removed, in order to prevent air from going into the baby.)

Technic of Exchange Transfusion

The umbilical cord is cut off square, about 1 cm. from the skin margin. If the umbilical arteries bleed, as they do occasionally, they are pinched off briefly with mosquito snaps. The umbilical vein usually bleeds a little, and is usually easily identified as the largest structure in the substance of the cord. It is commonly found at the periphery of the cord, at about 12 o'clock, but may be anywhere as a result of the natural gyrations of the umbilical vessels. When identified, one edge of the vein is picked up by a mosquito snap.

If the umbilical cord has been tied close to the skin at the time of birth, the original tie is removed, and the cord is cut off if necessary so that it is no more than about 1 cm. long. There is rarely if ever any difficulty in passing the cannula through the vein in the area where it has been tied off.

If the cord is completely dried out, it may be cut off flush with the skin margin, and the vein is picked up at this point, the cord tape being placed around the *skin* stump.

Visible blood clots in the distal part of the vein are removed with forceps.

The cannula, with its inlying plastic tubing, is gently inserted into the cut end of the umbilical vein. In order to avoid pushing a blood clot ahead of the cannula, it is first inserted for about 2.5 cm. Suction is then made with the syringe, and the cannula is very slowly withdrawn while the suction is continuously maintained. The cannula is then inserted gently as far as it will go, and suction is again applied. If blood does not flow freely, the cannula is again withdrawn slowly, with continued suction. If blood does come freely, the cord tape is tightened to make an airtight seal around the cannula, and the actual exchange is begun. The cannula usually goes in easily nearly to its hub, and is left in place throughout the exchange transfusion.

Not infrequently, the progress of the cannula stops after it has gone in about 2.5 cm. When this happens, slight caudad traction is applied to the vein, and the cannula is alternately withdrawn and gently pushed forward a few millimeters in various directions until the further course of the vein is located. Force must never be used because of the possibility of rupturing the vein. The cannula usually slides in with great ease once the channel is found. The small amount of plastic tubing that protrudes beyond the end of the cannula helps, by its softness and flexibility, to prevent damage to the vein, but it must not protrude more than about 0.3 cm., or the relative rigidity imparted by the steel cannula will be lost.

If more than fifteen minutes are spent in a fruitless attempt to get the cannula in, it is advisable to remove it, and explore with a blunt probe, again with great gentleness. The possibility should also be considered that the cannula has not been inside the lumen of the vein but in a false passage. The pearly-gray lining of the vein should be evident. Sometimes, a careful reinspection of the cord indicates that the vein is in quite a different location than had been supposed.

If all attempts fail after reasonable trial, the cord may be cut off shorter, or even flush with the skin margin, with re-exploration as described above. Actually, serious difficulty in putting in the cannula is very uncommon.

With the cannula in place and the cord tape tightened, gentle suction is applied with the syringe to remove blood from the baby.

If blood does not come instantly and with ease, very gentle caudad traction is applied to the umbilical cord by means of the cord tape (Fig. 6). This is the most helpful single maneuver in the performance of exchange transfusion via the umbilical vein.

If blood still does not come easily, or if it frequently stops, the cannula is moved in or out a few millimeters in an attempt to find a spot where the blood does come easily.

Occasionally, when the baby is large or the umbilical skin stump excessively long, the cannula seems to be not quite long enough to reach a spot where blood can be obtained easily. In this case the plastic tubing is pushed in about 1 cm. farther, after temporarily loosening the threaded end of the cannula. It is probably undesirable to insert the

plastic tubing more than 1 cm. beyond the tip of the cannula.

Suction applied by the syringe must always be gentle if blood is to be obtained. Rarely, it is necessary to use a smaller syringe than the 20-cc. syringe in order to control the amount of suction more accurately.

The end of the plastic tubing is usually within the umbilical vein, but may be in any of its branches, in the portal vein or in the ductus venosus. The introduction of the plastic tubing for more than about 7.6 cm. beyond the cut end of the umbilical cord, especially in small babies, may mean that the tip is in the heart, a theoretically undesirable location. The use of the umbilical-vein cannula, which should measure about 6 cm. from tip to hub, allows more accurate control of the tip of the tubing and should prevent the inadvertent insertion of the tubing farther than necessary.

At least 20 cc. should be removed from the baby before any blood is given. The ability to remove

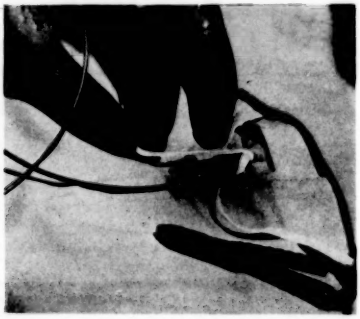


FIGURE 6. *Removal of Blood from the Umbilical Vein. The stump of the umbilical vein can be seen. The umbilical-vein cannula is in place, and cord tape is knotted around the cord stump. Very gentle traction is being applied via the cord tape, to facilitate the removal of blood.*

blood is the only certain indication that the cannula is actually in the vein. The reason for taking out at least 20 cc. is discussed below. It is our policy to remove at least 25 to 30 cc. before giving any, and then to give only 20 cc. at the most, for the first infusion. The first samples are saved for various tests.

The venous pressure may be measured directly with great ease, using the plastic tubing itself, after disconnecting the Tuohy adapter from the distal stopcock. A stainless-steel millimeter rule is placed vertically on the abdomen just above the umbilicus (Fig. 7) or on the xiphoid, and the tubing is held against it. Normal pressures are not greater than about 6 cm. of blood when measured at the xiphoid. Elevated venous pressures have been repeatedly demonstrated, particularly in babies with severe erythroblastosis, by Mollison and Cutbush[7] and by us. An increased venous pressure may be relieved with benefit to the baby by the removal of more blood than is put in. A deficit of 40 to 80 cc. may be established within a short time. The larger deficits are indicated particularly when the baby has been allowed to receive the maximum amount

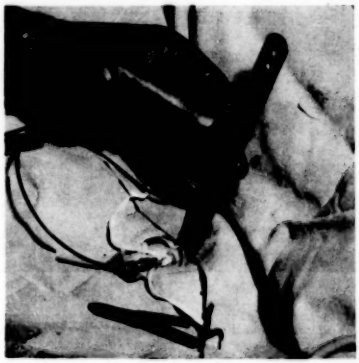


FIGURE 7. *Direct Measurement of Venous Pressure. A stainless-steel rule is being held vertically on the baby's abdomen just above the umbilicus, and the polyethylene tubing is held beside it. The level of the blood in the tubing can be seen at about 7.5 cm.*

of blood from the placenta at birth. We advise that the cord be clamped immediately after delivery, in every case in which the possibility of erythroblastosis is suspected, as a precautionary measure. DeMarsh et al.[8] have demonstrated that about 100 cc. of blood may be expected to be transferred from the placenta to the baby during a very few minutes after birth, when the cord is left unclamped. They also showed that such transfer of blood increases the circulating blood volume by about 60 cc., on the average, the discrepancy of 40 cc. being accounted for by rapid shift of plasma out of the circulation, with a resultant rise in hematocrit. Since such a large transfusion may be expected to overload an already embarrassed fetal circulation, the precaution of immediate clamping of the cord is well worth taking. We are certain, in retrospect, that some of the babies in our series have died primarily because of circulatory failure caused by

the administration of more blood than had been removed. It is our present policy, therefore, not only to clamp the cord immediately but also to measure the venous pressure, and to attempt to lower it when it is elevated, and also to take out in any case at least as much blood as is introduced during the exchange transfusion, so that the baby is never in positive balance as far as blood volume is concerned.

The exchange is continued by alternate withdrawal and introduction of equal amounts of blood; 20 cc. appears to be satisfactory in most cases,

FIGURE 8. *General View of Exchange Transfusion in Progress. The baby is entirely invisible in this view, but the donor blood (in the burette), exhaust tube and waste bucket are clearly visible. The suction apparatus is on the small table at the right, connected to a suction outlet in the wall.*

though larger amounts result in a more efficient exchange. In large babies who are in good condition, we have not infrequently used 40-cc. amounts. In small premature babies, or in babies who are in a precarious condition, smaller amounts (10 cc., perhaps) are preferable, being less likely to result in undesirable fluctuations of the venous pressure. The exchange is continued until a pint bottle of donor blood is used up. Wiener et al.[9] have advocated the use of large amounts of donor blood, up to 1000 cc. for a severely affected baby, but we prefer to stop at about 500 cc.* and to give a second exchange transfusion some hours later to babies who might be expected to profit by it. We have seen most gratifying results in a number of cases in which the transfusion was stopped after about 250 cc. had been exchanged in extremely sick babies who appeared unlikely to survive a continuation of the procedure.

A general view of the exchange transfusion in progress is presented in Figures 8 and 9.

*If an exchange of 250 cc. in a baby removes 58 per cent of its own blood, 500 cc. would remove approximately 82 per cent. An additional 500 cc. would remove only about 82 per cent of the remainder — that is, another 14.8 per cent. The law of diminishing returns makes the second 500 cc. less efficacious.

Donor Blood

The statistical implications of our study of the relation of the sex of the donor to the outcome of erythroblastotic babies treated by exchange transfusion[4] are such that we now use only blood from female donors. In the use of blood from female donors, care must be exercised to exclude by a routine screening test women whose serums contain significant amounts of Rh antibody.

The routine use of Group O donors is also recommended on the basis that the baby may be incompatible with the mother in the ABO system, as well as the Rh system, making the use of Group A or Group B blood potentially hazardous. It is recommended that the soluble A and B substances be added to Group O blood that is to be given to a baby of Groups A, B or AB, in the amount of 10 cc.† to the pint. If the baby has been demonstrated to be com-

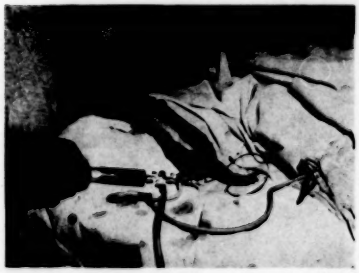


FIGURE 9. *Administration of Blood. The umbilical-cord stump cannot quite be made out in this view, but the end of the cannula is just above the operator's forefinger. The tubing emerging from under the towel clip comes from the burette of donor blood, and is seen connected to the apparatus by an ordinary glass adapter. The tube that disappears from the picture in the foreground is the exhaust tube. It can be seen that the top of the baby's abdomen is a few inches below the level of the top of the Hess bed.*

patible with the mother in the ABO system there is no reason to avoid giving, for example, Group A blood to a Group A baby. However, it is usually impossible to predict the blood group of the unborn baby (unless both parents are Group O) so that if a pint of blood is to be drawn ahead of time, or especially if blood is to be kept in readiness for any erythroblastotic baby who may come along, Group O blood is the only type to be considered as a general rule.

The donor blood should be Rh-negative in cases in which the mother of an erythroblastotic baby is

†Available from Sharp and Dohme, Philadelphia.

Rh-negative. There is no longer any doubt that Rh-negative blood is superior to Rh-positive blood on practical as well as theoretical grounds. If the mother is Rh-positive, blood that is not agglutinated by her serum should be used. This agglutination test must be performed by the albumin or the Coombs technic. If the mother's serum is not available for such testing, the baby's serum must be used, although it is a less reliable substitute.

Bank blood has been found satisfactory for exchange transfusions after as long as about two weeks' storage. It must be remembered, however, that the survival time of transfused red cells in the circulation is related to the age of the blood, and freshness is a desirable quality when there is a choice. Also, since the lowering of blood pigments in the baby is one of the principal aims of exchange transfusion[5] fresh blood, containing almost no free blood pigment, is highly desirable from this viewpoint.

It has been recommended by Mollison[10] that the donor blood be somewhat concentrated by the removal of some of the plasma to provide a red-cell count of between 5,000,000 and 6,000,000. We have done this with some regularity in the past. However, because it seems likely that any beneficial quality of blood from female donors resides in the plasma, we have not recently concentrated the donor blood in this manner. A relatively low red-cell count in the baby appears to have no ill effect during the first few days of life, and can be corrected later (though it is rarely necessary) by the administration of packed red cells. When a beneficial fraction of blood from female donors is isolated and concentrated, so that it can be given separately, the partial concentration of the donor blood by removal of part of the plasma will again seem desirable.

Cross-Matching Tests

Although in babies who are seriously ill it has been our custom to proceed immediately with exchange transfusion, using Group O, Rh-negative bank blood to which A and B substances have been added, without waiting for cross-match tests, a cross-match test is generally advisable when time permits and should be done in the following manner. A 2 to 4 per cent suspension of the donor's red cells is made in 20 per cent bovine albumin* or in her own serum; 0.1 cc. of this suspension is added, in a small tube (7 by 70 mm.), to 0.1 cc. of the baby's serum. The mixture is spun immediately, and if no agglutination is observed is incubated at 37°C. for fifteen to thirty minutes, spun down in a centrifuge at 1000 r.p.m. for one minute and examined grossly and microscopically for agglutination. Absence of agglutination in this "major" cross-match indicates compatibility. This technic is relatively protracted, so that preparations for exchange transfusion should not be delayed while the results of the cross-match are awaited. Actually, if the original typing of the donor can be relied on, there is little if any danger in omitting the cross-match in a newborn baby.

*Thirty per cent bovine albumin, 20-cc. vial, Armour Laboratories, Chicago, diluted with 10 cc. of physiologic saline solution.

General Consideration of Exchange Transfusion

The rapidity of the exchange transfusion is usually limited only by the baby's ability to handle the changes in blood volume and the amounts of citrate that are injected with the blood. Regarding the first point, a lively baby will usually indicate by restlessness or crying if blood is being injected too rapidly. A baby who is too sick to make such a response should be treated with caution, and the injection of blood should be very slow. It is our belief that the exchange of 500 cc. should take at least an hour, probably one and a half to two hours in very sick babies. So far as the citrate is concerned, the possibility of its calcium binding effect with resultant hypocalcemic tetany must be kept in mind continually.

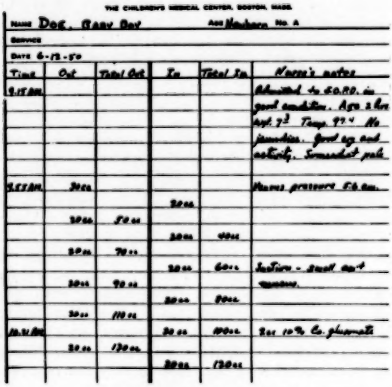
The apparatus should be constantly maintained as a closed system with respect to the baby's circulation, to avoid the possibility of entrance of air through an unguarded open plastic tubing. We have observed a serious though nonfatal air embolus when this precaution was not taken. Proper manipulation of the stopcock allows for complete protection in this respect. The only time the baby's circulation is allowed to communicate with the outside air by way of the plastic tubing is during the measurement of venous pressure, and then it is being carefully watched and the end of the tubing can be occluded with the finger if very low or negative venous pressure is evident.

If blood stops coming out, the probable reason is that blood is not getting into the plastic tubing. Measures to correct this situation have been discussed. If difficulty is encountered in the injection of blood, the usual reason is that the syringe is stuck because blood has got between the barrel and the piston. Fairly frequent rinsing of the syringe with physiologic saline solution to which a little heparin has been added will prevent this difficulty. Occasionally, a small clot in the apparatus is the cause of difficulty, and it will most frequently be found against the proximal end of the plastic tubing. In such a case, the Tuohy adapter may be disconnected from the distal stopcock, and the stopcock thoroughly rinsed while a finger is held over the open end of the plastic tubing.

Calcium gluconate, 10 per cent solution, should be kept ready in a separate syringe, so that it can be given quickly if desired. We have found, in many cases in which the baby is constantly restless and crying, that the injection of 1 or 2 cc. of calcium gluconate solution through the plastic tube immediately gives relief, and it seems most probable that such a response on the part of the baby is in-

dicative of potential tetany. We have observed carpal spasm in only 1 baby. The calcium should be injected *very* slowly, and the apparatus should have been cleared of blood by the injection of 1 or 2 cc. of saline solution before the calcium is given; otherwise the blood may be clotted by the strong calcium solution. It is our present policy to inject 1 cc. of 10 per cent calcium gluconate after each 100 cc. of donor blood.

The baby should be under the close and constant supervision of a nurse, who must be prepared to administer pharyngeal suction and who should be responsible for the presence of a mechanical suction


THE CHILDREN'S MEDICAL CENTER, BOSTON, MASS.

Name Doe, Baby Boy Age Newborn No. A

Service

Date 6-13-50

Time	Out	Total Out	In	Total In	Nurse's notes
9:15 AM					Admitted to C.M.C. in good condition. Age 2 hrs Wgt. 7# Temp 99.4 No jaundice. Good cry and activity. Semisolid pab
2:15 PM	30 cc		20 cc		Plasma pressure 56 mm.
	20 cc	50 cc			
	20 cc	70 cc	20 cc	40 cc	
	20 cc	90 cc	20 cc	60 cc	Suction - small amt mucous.
	20 cc	110 cc	20 cc	80 cc	
10:30 PM			20 cc	100 cc	2 cc 10% Ca gluconate
	20 cc	130 cc			
			20 cc	120 cc	

FIGURE 10. *Score Sheet.*
Note that each entry is put on a separate line.

apparatus in good working order. Oxygen should be administered constantly, preferably by means of a soft-rubber, mask-type cone, which fits the contours of the baby's face. The nurse should keep track of the temperature within the incubator, to avoid overheating as well as excessive cooling of the baby. Stimulant drugs are rarely necessary, and are of doubtful value.

A score keeper, usually the nurse who is watching the baby, is of considerable help. Figure 10 shows the type of record we keep during the course of the transfusion. It will be noted that a separate line is used for each new entry, which usually avoids considerable confusion.

Completing the Transfusion

When the donor blood is used up, or it is decided to stop the transfusion for any other reason, calcium gluconate is given *very* slowly through the plastic tubing after clearing the blood out with a little saline solution. We customarily give 2 cc. of the 10 per cent solution over a period of five minutes. We also give 2 cc. of vitamin K solution mixed with the calcium solution, though we are not convinced of its value. The cord tape is tightly tied as the cannula is withdrawn, and a dry sterile dressing is applied. (If a second exchange transfusion is contemplated the cord dressing may be wet with 1:2000 Zephiran solution, and kept wet by occasional application of a little sterile saline solution, in order to keep the cord from drying out too much.) Penicillin is given routinely in a dosage of 100,000 units, once daily for three days, for prophylaxis, and sodium sulfadiazine solution is injected intramuscularly in a total dose of about 150 mg. per kilogram of body weight, in divided doses over the first twenty-four hours or so. Oxygen is given in high concentration for five days, and crude liver extract (2 units per cubic centimeter) is given intramuscularly in doses of 1 cc. three times a day for five days. The oxygen and liver are discontinued before five days if the jaundice has faded. The use of oxygen and liver is mentioned not because there is any indication that they help prevent kernicterus (though such an effect is possible on a theoretical basis) but because it has been part of a routine for two years from which we do not dare to deviate at present because the end results have been so favorable.

The babies are examined carefully at least once a day to estimate the degree of jaundice of skin and urine, and to note the presence or absence of opisthotonos, general alertness and a normal Moro reflex, since it is reasonably certain that if the baby remains alert and supple and continues to have a normal Moro reflex during the first five days of life, it does not have, and will not develop, kernicterus. We have been greatly impressed with the rapidity of fading of jaundice after exchange transfusion. At the end of four days there is usually no detectable jaundice of the skin or scleras.

Feedings are usually started at about twenty-four hours of age, beginning with 5 per cent glucose in water in small but increasing amounts for perhaps three feedings, and then gradually substituting a dilute evaporated-milk and Karo formula (12 to 15 calories per ounce) over the next three feedings, and changing to a stronger evaporated-milk and Karo formula (about 20 calories per ounce) after about six days. Most of the babies have been formula fed, because of fear that if fed at the mother's breast they will absorb Rh antibodies from the milk. This fear is probably unwarranted, since it is probable that the baby does not absorb Rh antibodies after about three days of age. The blood count is repeated when the baby is four or five days of age, and a small transfusion (approximately 25 cc. per kilogram of body weight) of packed red cells is given as indicated (red-cell count of 3,500,000 or less) at seven to ten days of age. Almost all the babies go home with their mothers at five to twelve

days of age. The blood count is then followed at intervals of two or three weeks for the next four to six weeks. A small transfusion of packed cells is given if the red-cell count falls below about 2,000,000 (hemoglobin below about 7 gm.) or if the baby is doing poorly; 5 to 10 per cent of babies have required subsequent transfusions after discharge from the hospital.

Indications for Exchange Transfusion

It might be argued that all Rh-positive babies of sensitized Rh-negative women should be treated by exchange transfusion because of the unpredictability of erythroblastosis fetalis and the ease of performance of the procedure. We are still attempting to separate babies who require no treatment of any kind from those who would have required one or more small transfusions if not treated by exchange transfusion. The evidence[11] indicates that between 10 and 20 per cent of Rh-positive babies born to sensitized Rh-negative women would have no jaundice or anemia of such severity as to warrant a diagnosis of erythroblastosis fetalis on purely clinical grounds (though they almost invariably have a positive direct Coombs test). The decision, at the time of birth, whether or not a particular baby will have no clinically demonstrable disease is another matter, however. On the basis of our past experience an exchange transfusion is done immediately under the following conditions:

If the baby (less than twenty-four hours of age) has clinically apparent erythroblastosis fetalis on the basis of early jaundice, hepatosplenomegaly, pallor, edema or petechiae, or a red-cell count of less than about 4,500,000 with a hemoglobin value* of less than about 13.5 gm. per 100 cc.

If the baby is Rh-positive as demonstrated by direct testing or a positive direct Coombs test,[12] and the mother's titer of Rh antibody was 1:16 or higher at some time during pregnancy. It must be remembered that about 10 per cent of erythroblastotic babies are typed as Rh-negative by all the usual typing methods when they should have been typed as Rh-positive. A positive direct Coombs test indicates indirectly that the baby *is* Rh-positive when the mother's serum is known to contain Rh antibodies.

If the baby is Rh-positive, and there is an unfavorable past history, particularly a history of kernicterus in a previous sibling, regardless of the titer level. This criterion is based on the conclusion that kernicterus is preventable in some, if not all, cases by exchange transfusion. We have done exchange transfusions in babies who already had signs and symptoms of kernicterus without apparent benefit, but are not sure that exchange transfusion may not be beneficial in some babies with early signs of kernicterus.

If the Rh-positive baby is immature (for example, a baby with an estimated gestation of less than thirty-eight weeks). This criterion is based on the likelihood of kernicterus in immature, especially in immature *male*, babies.[13]

A second exchange transfusion has been given, twelve to twenty-four hours after the first one, whenever the likelihood of kernicterus seems high. The immature male infant of a highly sensitized mother who has had a previous baby with kernicterus is the most likely candidate for this. We also consider kernicterus most likely to develop in the baby who becomes intensely jaundiced in the first twelve to twenty-four hours after exchange transfusion done at birth. In the 27 cases in which we have attempted a second exchange transfusion, we have again used the umbilical vein, with complete technical success in each case. In one of these babies — a premature baby delivered by cesarean section because of other complications — kernicterus developed. Our present policy is not to wait for intense jaundice, but to do a second exchange transfusion whenever the jaundice increases to "moderate" after an initial transfusion.

When erythroblastosis occurs as a result of blood-group incompatibility other than the usual Rh factor, it is generally no different qualitatively from that caused by Rh incompatibility. Unless there has been a previous erythroblastotic baby in such a family, the diagnosis will not have been made until after it has been suspected on purely clinical grounds. (The diagnosis should always be suspected when jaundice or anemia appears during the first two days of life.) The indications for exchange transfusion of such a baby are thus quite simple according to the rules outlined above, and the only problem is to find the right type of blood. The simple rule for selecting blood for such a baby is to take only Group O donors, test the red cells against the mother's (preferably) or baby's serum by the albumin technic described above,† and use the donor whose red cells are not agglutinated. The least common type of blood that will ever be needed under such circumstances (that of a homozygous Rh-positive donor) is found in 20 per cent of the population.

Results of Exchange Transfusion

From November 9, 1946, to August 1, 1950, 391 exchange transfusions were attempted by the members of this group,‡ only a few of them having been done at hospitals other than the Children's Hospital, the Boston Lying-in Hospital and Richardson House.§ The following data have no statistical

*By the alkaline hematin method, using an accurate photoelectric colorimeter.

†The Coombs test[12] is superior when done by an experienced technician.

‡We are indebted to the following physicians, each of whom did a number of the transfusions while a member of our special team: Crawford H. Hinman, Victor C. Vaughan, III, William L. Caton, Jr., Francis R. Lane, Lloyd I. Sexton, Joseph B. Watrous, Jr., William Pfeffer, Jr., Ellsworth Twible and Dante DelCampo.

§Private wards of the Boston Lying-in Hospital.

value but represent simply a compilation. Statistical analyses form the basis of other reports.[4, 5]

Table 2 summarizes the amount of blood removed through the umbilical vein in 391 attempted exchange tranfusions in 362 different babies. In 13 cases less than 200 cc.* was removed because of technical difficulties. These cases are summarized in Table 3. Only 1 of these babies was very sick.

TABLE 2. *Amount of Blood Removed Through the Umbilical Vein.*

Amount of Blood	No. of Cases					Totals
	1946	1947	1948	1949	1950*	
cc.						
None (complete failure)	1	3	0	2	0	6
25 to 149	0	2	4	3	1	10
150 to 199	0	1	4	3	0	8
200 to 299	0	5	11	2	2	20
300 to 399	2	18	15	17	10	62
400 and over	5	58	37	99	86	285
Totals	8	87	71	126	99	391

*Up to August 1.

TABLE 3. *Data on Cases in Which Exchange Transfusion Through the Umbilical Vein Was Technically Unsuccessful.*

Case No.	Amount Removed	Age of Baby	Remarks	Outcome
	cc.	*hr.*		
3	0	15	Mild disease	Recovery
23	0	18	Exchange done through saphenous vein	Recovery
38	0	15	Mild disease	Recovery
58	150	3	Mild disease	Recovery
74	0	4	Exchange done through femoral vein	Recovery
102	113	3	Moderate illness	Recovery
105	190	3	Baby not sick on entry	Kernicterus
133	25	1	Very mild disease	Recovery
163	100	2	Very mild disease	Recovery
170	0	6	Exchange done through saphenous vein	Recovery
263	0	17	Cord cut off and cauterized	Kernicterus
275	65	14	Baby moribund	Death at 18 hr.
284	55	1	Exchange done through saphenous vein	Recovery

It has been quite evident that technical difficulties in removing blood are more common in mildly affected babies. In 11 other cases the procedure was stopped electively before 200 cc. had been removed. There have been no technical failures in the last 100 cases. The use of the umbilical-vein cannula has greatly reduced the incidence of technical difficulties.

Table 4 summarizes the ages of the babies at the start of the procedure. Having tried the procedure in a number of babies over twelve hours of age we have found no difference in degree of technical difficulty in these older babies. Two babies had exchange transfusion through the umbilical vein at the age of six days, without difficulties. The procedure has not been attempted through the umbilical vein in older babies. In each case the vein has been entered through the cord stump, without cutting down.

Table 5 summarizes the outcome in babies with erythroblastosis fetalis caused by anti-D. Twenty-four had two, and 2 had three exchange transfusions. Of the 12 babies who died during the exchange transfusion, 11 were desperately sick at the start, most of them being hydropic. In the other (Case 29), sudden death was not explained pathologically but was blamed on the procedure.

Eleven additional erythroblastotic babies, not included in Table 5, were treated by exchange transfusion. Four of these were caused by anti-A, with 3 recoveries and 1 case with kernicterus. Four whose disease was caused by anti-c (anti-Hr′) recovered. There was 1 case each of anti-B and anti-E, with recovery in both. In 1 case in which the antibody has not been identified, the baby had the usual clinical symptoms and a positive Coombs

TABLE 4. *Age of Babies at Start of Exchange Transfusion.*

Age	No. of Cases				
hr.	1946	1947	1948	1949	1950
Less than 3	5	32	32	48	39
3 to 6	1	28	24	21	13
6 to 12	1	5	12	22	11
12 to 24	1	14	2	22	17
24 to 48	0	1	0	8	14
48 to 72	0	0	0	1	1
72 to 96	0	0	0	0	1
96 or over	0	0	0	0	2
Unknown	0	7	1	4	1

TABLE 5. *Outcome of Erythroblastosis Fetalis Caused by Anti-D in Babies Treated by Exchange Transfusion, Including "Failures."*

Outcome	No. of Cases					Total
	1946	1947	1948	1949	1950	
Recovery, with no sequelae	6	64	56	94*	66‡	286
Death during transfusion	0	3	3	4	2	12
Death after transfusion, before 24 hr.	0	3	1	6	3	13
Death after 24 hr. (no kernicterus)	2	6	3	3†	3§	17
Kernicterus, with patients living or dead	0	8	6	2	3¶	19
						347

*10 babies had a second exchange transfusion.

†1 baby had a small repeat exchange transfusion at the age of twenty-one hours, undertaken primarily for relief of high venous pressure.

‡12 babies had a second exchange transfusion; 2 of these had a third exchange transfusion.

§2 babies had a second exchange transfusion; both were hydropic on admission.

¶1 baby had a single exchange transfusion on the second day of life — clinical evidence of kernicterus was well established at the time of admission. The second baby received a second exchange transfusion eighteen hours after the onset of symptoms of kernicterus, without alteration of the course. The third baby was premature and developed kernicterus after a second exchange transfusion had been done.

*An exchange of 200 cc. gives a replacement of about 50 per cent in the average-sized newborn infant.

test. Four babies that did not have erythroblastosis received exchange transfusion. One of these was a six-day-old baby with acute acquired hemolytic anemia of unknown etiology; 2 transfusions were done because of undiagnosed hemorrhagic disorder in previous siblings. The fourth patient (Case 62) proved to be an apparently normal baby except for some staining of the vernix from anoxia.

Summary

Exchange transfusion is the treatment of choice for babies with erythroblastosis fetalis, since it has been shown that its use has brought about a decrease in mortality, along with a marked reduction in the incidence of kernicterus.

The technical details of a method of exchange transfusion through a single plastic tubing, inserted into the umbilical vein, are presented, as well as an outline for aftercare.

The indications for exchange transfusion of a sick, or potentially sick, erythroblastotic baby are listed.

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OCCURRENCE OF CONVULSIVE SEIZURES DURING TREATMENT OF ASTHMA WITH CORTISONE ACETATE*

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CORTISONE is being used in a wide variety of clinical conditions. This drug has profound physiologic effects, and occasional undesirable reactions are to be expected.

Several observers have noted convulsive seizures in patients receiving the adrenocorticotrophic hormone (ACTH) of the pituitary body, which is closely related in its effects to Cortisone, but to our knowledge no such case is recorded in the literature. Some of these patients suffered from diseases that are known to cause seizures occasionally. In others the seizures have been ascribed to contamination of the preparation with hormone from the posterior pituitary body or to cerebral edema resulting from retention of salt and water by the kidney or hypertensive encephalopathy. To a lesser degree, Cortisone also causes retention of salt and water by the kidney, and if seizures can indeed arise on this basis, the drug might be expected to cause them occasionally. There has been only one such case reported to date,[1] the details of which are not given. Furthermore, this patient had disseminated lupus erythematosus, a disease known to cause seizures.

The importance of knowing whether Cortisone can give rise to seizures is obvious, and for this reason the following case is reported. The patient had severe asthma and, after receiving Cortisone for eleven days, developed a number of seizures under circumstances strongly indicating that the drug was responsible.

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Case Report

R. D., a 23-year-old man, had had asthma since infancy of sufficient severity to limit his activities markedly. He finished high school at the age of 18, but because of the severity of the asthma did not engage in any regular occupation thereafter. He was first seen in the summer of 1948, when physical examination showed pigeon-breast deformity of the chest, with scoliosis, distant breath sounds and numerous musical rales. Cyanosis was also present. Examination was not otherwise remarkable. Skin tests showed pronounced reactions to many allergens, including pollens, animal danders, molds and house dust. Tests with inhaled allergens by a method previously described[2] showed clear-cut pulmonary reactions to several allergens. He was admitted to the hospital in December, 1948, for 3½ weeks and improved markedly, but continued to require medication for asthma. He was treated with injections of allergenic extracts during

1949, with questionable benefit, and continued to have asthma during the winter of 1949-1950. In April, 1950, he still had severe asthma, for which he had been receiving aminophylline suppositories and Isuprel by hand nebulizer several times daily.

The past history revealed the usual childhood diseases. There had been no previous seizures or suggestive episodes. Headaches had been very infrequent. Except for asthma, the patient had been in good health.

A sister had asthma, and the patient's father had hay fever. There was no family history of epilepsy or seizures.

Table 1 presents some of the changes that occurred during treatment with Cortisone acetate.* This was preceded for 3 days by injections of a placebo consisting of a suspension of cholesterol. Cortisone and the placebo were self-administered by intramuscular injection in doses of 50 mg. every 6 hours, making a daily dose of 200 mg. No instructions were given regarding the daily intake of salt. Treatment with Cortisone was begun on April 5, and 3 days later there was subjective improvement, which increased during the next 7 days and was accompanied by a ravenous appetite, decreased cough and marked lessening of dyspnea on exertion. During this period there was a gain in weight, a rise in the white-cell count and a fall in the number of circulating eosinophils, as shown in Table 1. Demonstrable peripheral edema was absent during the entire period, and there was no significant change in blood pressure. At this time there were no audible wheezes in the chest. On April 14 the patient was permitted to visit his family about 100 miles from Boston. He felt better on April 15 than he had at any time in his memory. He spent a very active day going fishing and driving with friends. He ate more than usual, including pickles, potato chips and pretzels, and had 3 glasses of ale with added salt in the evening (he stated that he had always salted his food heavily). At about 10:00 p.m. while driving in an old car (which rode very badly) he developed a mild headache, which he ascribed to the exhaust fumes. His companions complained of the smell also, but did not develop headaches. He returned home at about midnight and went to bed after taking his Cortisone as usual. He awoke the next morning with a headache, for which he took 2 Anacin tablets; he did not take his Cortisone, and ate no breakfast. According to the patient's father, there was some nausea and vomiting. He stayed in bed, and at about 10:30 a.m. while the family were downstairs they heard a noise as though someone were falling, and upon investigating found the patient on the floor, unconscious, deeply cyanotic and with swelling of the face and lips. The nebulizer was in the basin, suggesting to the family that he had just been using it. They put him in bed and called a physician, who arrived 20 or 30 minutes later and found the patient still unconscious and gave him some epinephrine. The doctor reported that the patient had been incontinent of feces and urine, but on examination all reflexes were present and there were no localizing neurologic signs. The blood pressure was 90/70. The patient quickly recovered consciousness and felt so well that he was persuaded with difficulty to go to a nearby hospital. At about 12:30 p.m., while being examined in the sitting position, he complained of a very intense headache on the left. He lay down and then had a seizure, which began with marked deviation of both eyes to the right followed by clonic movements of the arms and legs, more marked on the right. During this seizure he was unconscious but not incontinent, and he seemed to recover completely at the end of about 2 minutes. No medication was given. A lumbar puncture done shortly thereafter yielded clear spinal fluid under a normal pressure, containing no cells and with a protein of 29.6 mg. per 100 cc.

We saw the patient at about 4:30 p.m., when he was conscious and oriented but somewhat slow in his responses, and was complaining of a fairly severe but symmetrical frontal headache, which became more intense as time went on. His face seemed fuller than when he had been seen 2 days before. There was no evidence of trauma. Upon careful questioning later, the patient denied the occurrence of head injury at any time. The deep tendon reflexes were hyperactive and equal throughout. There was no stiffness of the neck. The eyes and eyegrounds were normal except for increased tortuosity of the veins, which had been present 1 year previously. The plantar responses were normal, and the abdominal reflexes were present and equal. There were a few rhonchi and musical rales throughout the chest, and moist rales in the right lower anterior part of the chest. There was no leg edema. During the examination, the patient became increasingly nauseated, and the headache became more intense but was not lateralized. The respirations became deeper and slower. During a period of 2 or 3 minutes, he became confused and finally apparently lost consciousness. For about 30 seconds his eyes deviated markedly to the right. He had clonic or convulsive movements during this episode. The blood pressure was 130/90. He slowly recovered, but for about ½ hour he was nauseated and vomited small quantities of yellow fluid.

Because of the possibility of a pulmonary infection, he was given 100,000 units of aqueous penicillin intramuscularly, preceded by cultures of the nose and throat, which later yielded normal flora, and a blood culture, which proved to be sterile. He was also given codeine, atropine and phenobarbital and was sent to the Massachusetts Memorial Hospitals by ambulance. He reached the hospital without further incident.

The physical findings on admission were unchanged. Laboratory studies showed a normal urine. The blood Hinton reaction was negative. The sedimentation rate was 7 mm. per hour, and the hematocrit 49 per cent. The hemoglobin was 15.6 gm. per 100 cc., and the white-cell count 22,500, with 78 per cent neutrophils and no eosinophils. The nonprotein nitrogen was 37 mg. per 100 cc., and the sodium 144 milliequiv., potassium 4.5 milliequiv., carbon dioxide content 33.6 milliequiv., and chloride 89.2 milli-

Table 1. *Effects of Cortisone Therapy.*

Date	Amount of Cortisone	Weight	Blood Pressure	White-Cell Count	Circulating Eosinophils	Remarks
April, 1950	*mg./day*	*lb.*		*x10³*	*per cubic millimeter*	
4	—*	112	106/80	9.5	88	—
5	100	113	105/70	8.8	209	—
6	200	112	100/80	14.1	264	—
7	200	111	—	17.2	121	—
8	200	111	110/80	17.9	55	—
9	200	—	—	—	—	—
10	200	113	120/80	19.3	22	—
11	200	114	110/70	21.6	11	—
12	200	115	110/74	16.0	11	—
13	200	116	110/80	17.9	22	—
14	200	117	120/80	18.1	11	—
15	200	—	—	—	—	Patient at home and feeling well
16	0	—	—	—	—	Seizures began

*Placebo.

*Kindly supplied by Merck and Company, Incorporated, Rahway, New Jersey, and hereinafter referred to as Cortisone.

equiv. per liter. On the following day the fasting blood sugar was 100 mg., and the total protein was 6.2 gm. per 100 cc., with an albumin of 3.8 and a globulin of 2.4 gm. per 100 cc. An electroencephalogram on April 18 revealed marked alpha asymmetry and some rhythmic slow activity, with no focal abnormality. X-ray films of the skull were normal.

The headache was still present and about 1 hour after arrival (about 11:30 p.m.) the patient had a fourth episode of unconsciousness lasting about 20 minutes, characterized by deep, slow respirations and cyanosis. However, no convulsive movements were observed. The blood pressure during this attack was normal. Recovery was gradual, and he felt well on the following morning. He received no Cortisone on this day but was given 50 mg. on the next day and 100 mg. daily thereafter. He was discharged on April 20 and continued to take 100 mg. of Cortisone daily for 3 weeks, after which the dose was gradually decreased.

There was a moderate increase in asthma on the day after the seizures (April 17). In the course of the next week a respiratory infection also developed, with a low-grade fever, productive cough and a raw feeling in the chest, described as quite different from the usual asthmatic symptoms. He also had increased sweating and felt weak. Sputum culture on April 26 yielded pneumococci in abundance, but there was no x-ray evidence of pulmonary involvement. Treatment with penicillin was begun on April 27, after which the manifestations of infection gradually subsided.

On May 15, at a time when the dose of Cortisone was gradually being decreased and the patient was receiving 50 mg. a day, tremor of the fingers and lid-lag were noted, but there was no tremor of the tongue. On questioning, he stated that while fishing 1 week earlier, he had had difficulty baiting hooks because of tremor of the hands. On May 17 the uptake of radioactive iodine by the thyroid gland was 23.5 per cent of the administered dose. Cortisone was stopped on May 19, and 2 weeks later the tremor and lid-lag were decreased but still present; 5 days after this they were no longer demonstrable. At this time asthma had returned to a degree approximately equal in severity to that present before treatment with Cortisone was begun. An electroencephalogram on July 12, while the patient was receiving 80 mg. of ACTH* daily, was interpreted as normal.

Discussion

There seems to be little doubt that Cortisone in the dosage given (200 mg. daily) was having a pronounced effect at the time that the seizures occurred. This is supported by distinct improvement in the asthma, marked feeling of well-being, increased appetite, rounding of the face, gain in weight and eosinopenia and leukocytosis. It seems reasonable, therefore, to ascribe the occurrence of the seizures to either a direct or an indirect effect of Cortisone.

Other possible causes of seizures seem unlikely. There was no history of head injury. Infectious, neoplastic or vascular lesions of the central nervous system were improbable in view of the normal findings on lumbar puncture, the absence of neurologic abnormalities between seizures and the subsequent course. The normal spinal-fluid pressure, and the absence of hypertension seem to rule out hypertensive encephalopathy, which has been suggested as a cause of seizures in patients receiving ACTH. Idiopathic epilepsy cannot be excluded, but no seizures had occurred at any time previously, and the family history was negative for epilepsy. The possibility of an unusual reaction to Anacin, Isuprel or aminophylline, which the patient had taken, seems to be excluded by their failure to produce any untoward effects before or subsequently.

The seizures may have been a direct effect of Cortisone on the cerebral cortex, a possibility that is supported by the reported capacity of Cortisone[3] and ACTH[4] to produce changes in the electroencephalogram; indeed, an electroencephalogram taken four days after the seizures, although not clearly abnormal, showed an increase in slow-wave activity, which was more marked than when the patient was not receiving Cortisone. Another possible cause is cerebral edema arising from retention of salt and water induced by Cortisone. That retention of water occurred in this patient prior to the seizures is indicated by a weight gain of about 5 pounds during the first ten days of treatment, and there may have been a further gain in weight on the eleventh day, although the patient was not weighed. Furthermore, on this day, the one preceding the seizures, the salt intake was exceptionally high, and considerable retention of water may have occurred. Finally, the severe headache that preceded the seizures may have been a manifestation of cerebral edema, which is not excluded by the absence of demonstrable peripheral edema, and by the presence of a normal blood sodium. Latent epilepsy may have been stirred up by a direct effect of Cortisone on the cerebral cortex, by cerebral edema due to retention of salt and water or by some other mechanism related to the effect of Cortisone, any of which might fail to produce seizures in the absence of latent epilepsy. The intake of alcohol on the preceding evening, although moderate, may have contributed to the production of seizures, as is often observed in patients with epilepsy.

Resumption of treatment with Cortisone in a dose of 100 mg. daily — half that which he received previously — was well tolerated, but was less effective in controlling the asthma and failed to cause a significant reduction in eosinophils. The absence of headache or seizures may have been due to the lower dosage of Cortisone, but restriction of salt at this time may also have been a factor. However, an interesting and possibly related phenomenon was the occurrence, about twenty-one days after the seizures and about eighteen days after treatment with Cortisone was resumed, of tremor of the hands. This was clearly evident one week later on examination, and at this time lid-lag was also present. Other findings suggestive of hyperthyroidism were absent, and these manifestations, the significance of which is difficult to assess, disappeared after treatment with Cortisone had been discontinued.

If the seizures in this patient were indeed caused directly or indirectly by Cortisone, the seizures observed by others in patients receiving ACTH may have been due to an effect of the hormone itself rather than to some complication of the disease under

*Kindly supplied by Armour Laboratories.

treatment or to the posterior pituitary hormone supposedly present in some preparations of ACTH.

Summary

Four seizures occurred in a space of twenty-four hours during treatment of a case of bronchial asthma with Cortisone. No cause of the seizures other than a direct or indirect effect of the drug could be established. Retention of salt and water produced by Cortisone is suggested as a cause.

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SUPPURATIVE PYLETHROMBOPHLEBITIS AND MULTIPLE LIVER ABSCESSES FOLLOWING ACUTE APPENDICITIS*

Report of a Case with Recovery

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IN THE course of suppurative conditions of abdominal structures drained by the portal system, the development of an ascending phlebitis with embolic liver abscesses is an event to be feared by the internist and the surgeon. Although the appendix is most frequently the starting point, the process may be initiated by suppuration in the gall bladder, diverticula, intestine, pelvic structures or hemorrhoids. Its frequency varies considerably in the published reviews, ranging from 0.09 to 0.82 per cent of the cases of acute appendicitis.[1, 2] Soro,[3] in 1948, compiled 17,000 cases of acute appendicitis from the European literature from 1905 to 1935, and found a mean incidence of 0.40 per cent. A review of the surgical pathological and autopsy indexes at the Mary Hitchcock Memorial Hospital, covering the period from January, 1943, to January, 1950, failed to reveal another case of suppurative pylethrombophlebitis. During this interval, 495 cases of acute appendicitis were diagnosed pathologically, and 820 autopsies were performed. The following case emphasizes the difficulty that may be encountered in early correct diagnosis of this rare condition, and illustrates the effect of combined medical, surgical and antimicrobial therapy.

Case Report

A. R. C. (M.H.M.H. A-61428), a 43-year-old man of Italian descent, was admitted to the Mary Hitchcock Memorial Hospital on July 7, 1948, because of chills and fever for 14 days. Approximately 16 days previous to entry, he noted generalized crampy lower abdominal pain, which was rapidly and completely relieved by a soapsuds enema. However, later in the day he complained of nausea, vomiting, black and foul-smelling watery stools, and fever. On the next day he took some Epsom salts, "to finish cleaning me out." The abdomen was merely "sore," and he felt somewhat better after the cathartic. Fourteen days before admission he observed malaise and his first shaking chill. Until admission, he had recurring chills, fever and drenching sweats. Malaise and steady weight loss continued, but the mild abdominal complaints soon disappeared. His referring physician had obtained normal chest roentgenograms, and blood agglutinations for *Salmonella typhosa* and brucella organisms were negative. Procaine penicillin, 300,000 units intramuscularly daily for 1 week before admission, had been totally ineffective in altering the gradually downhill course. The past history, family history and system review were irrelevant. There had been no previous operations or trauma.

Physical examination upon admission revealed a well developed and fairly well nourished man complaining only of malaise and weakness.

The temperature was 99.6°F. by mouth, the pulse 78, and the respirations 22. The blood pressure was 80/50.

The low blood pressure was obtained immediately after a drenching sweat. No jaundice, rash or petechiae were seen. Both membrana tympani showed old perforations, without signs of active infection or discharge. The pharyngeal mucosa was slightly injected. No local or generalized lymph node enlargement was noted. The lungs were clear to percussion and auscultation, and examination of the heart was negative. Abdominal examination did not reveal tenderness, spasm, organs, masses or hernias. Neurologic and rectal examinations were negative.

Urinalysis was negative except for 0.01 gm. of albumin per 100 cc.

Examination of the blood showed a red-cell count of 3,380,000, with a hemoglobin of 9.3 gm. per 100 cc. (Klett method), and a white-cell count of 20,500, with 80 per cent neutrophils, 12 of which were stab forms. Roentgenograms of the chest were normal. A preoperative abdominal roentgenogram was normal. A blood serologic test for syphilis (Mazzini test) was negative. Shortly after admission, a blood Fouchet test was negative, and the icteric index was normal. Subsequent laboratory data are presented below and in Figure 1. An electrocardiogram revealed sinus tachycardia.

On admission, various diagnoses were considered: brucellosis, bacterial endocarditis, malaria, enteric fever and miliary tuberculosis. During the 1st hospital week, the course was characterized by frequent sharp chills, a temperature of 100 to 106°F. and drenching sweats. No malarial parasites were seen on repeated blood smears. Stool cultures failed to show enteric pathogens. Blood agglutinations for *S. typhosa*, the paratyphoid group and *Brucella abortus* were repeatedly negative. By the end of the 1st week, the white-cell count had risen to 35,700, and an extremely tender liver was easily felt. Blood cultures taken on the 3rd and 4th hospital days

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exhibited *Streptococcus viridans* and *Staphylococcus albus*. A blood culture taken on the 9th hospital day showed *Str. viridans* and *Escherichia coli*. With these new findings at hand, it was suggested that the patient had pylephlebitis and multiple liver abscesses secondary to appendicitis.

In the 2nd hospital week, administration of large doses of penicillin and streptomycin was begun (Fig. 1), each drug having been demonstrated to be effective in vitro against one of the organisms isolated from the blood. Three whole-blood transfusions of 500 cc. each were given as supportive therapy. The white-cell count dropped to 14,000. The icteric index rose to 18 units, and the thymol turbidity was 6 units. The septic temperature swings merely lowered their average value by 1°F. By the end of the 2nd hospital week it appeared that medical measures were inadequate to control the infection, and surgical exploration was decided upon.

On July 20 exploratory celiotomy was performed by Dr. M. Dawson Tyson. The liver was found to be enlarged and to contain multiple scattered areas of induration. General exploration was negative until a firm mass was noted in the region of the cecum. This proved to be omentum adherent to the inflamed distal portion of the appendix and an area of periappendicitis. A small amount of pus was walled off between the omentum and the appendix. Once this organ had been removed, attention was directed to a cord-like and indurated mass extending upward toward the root of the mesentery. This structure was identified as the thrombosed ileocolic vein, along which were noted several abscesses. The thrombotic process extended 5 cm. above the junction of this vein and the superior mesenteric vein. A probe could be passed with ease above this point. Palpation of the portal vein did not reveal involvement. Because of the proximity of the superior mesenteric artery, ligation could not be accomplished at the usual distance above the upper limit of the thrombosis. The section was therefore made near this area, free bleeding being noted from the proximal cut end of the vein prior to ligation. The ligatien involved either the main superior mesenteric vein or a large branch of it. As much as possible of the diseased veins was resected. Further exploration of the liver revealed innumerable small, yellowish, indurated areas and one larger abscess. No pus could be aspirated from any of these regions. After a biopsy of the liver had been obtained abdominal closure was effected without drainage. The patient tolerated the procedure well.

Culture of the exudate from the lumen of the ileocolic vein showed *Str. viridans* and *Esch. coli*. Pathological examination of the tissues removed at operation demonstrated organizing liver abscesses, suppurative thrombophlebitis, chronic suppurative appendicitis and periappendicitis.

The immediate postoperative course was satisfactory. An abdominal roentgenogram on the 2nd postoperative day revealed moderate gaseous distention. Five grams of sodium sulfadiazine was given intravenously at the end of the operation. The dose was repeated the next day, but the administration of this agent was discontinued because of transient microscopical evidence of hematuria, crystalluria and oliguria shortly after the second dose had been given. The administration of penicillin and streptomycin was continued. Streptomycin was stopped on the 5th postoperative day, possibly prematurely, for on the next day evidence of sepsis returned, as manifested by a chill and a temperature of 103.4°F. A blood culture taken at the time of this chill revealed *Str. viridans*. After the readministration of streptomycin at its previous dosage level, the temperature slowly fell, reaching constantly normal values by the 13th postoperative day. The white-cell count, icteric index and blood Fouchet test slowly returned to normal values. Penicillin and streptomycin were discontinued, without return of fever, on the 19th postoperative day. Splenomegaly, peripheral embolic phenomena, significant cardiac murmurs and ascites were never observed. After a period of steady improvement, the patient was discharged home for convalescence on August 21, after 45 days of hospitalization. Attempts at follow-up study were unsuccessful.

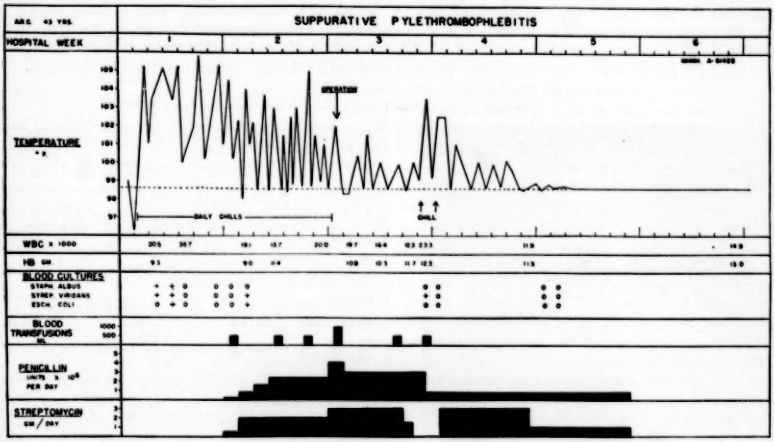

FIGURE 1. *Clinical Course Correlated with Laboratory Data and Therapeutic Procedures.*

DISCUSSION

This case typically demonstrates the picture of suppurative pylephlebitis with embolic liver abscesses. The condition was confused with brucellosis, bacterial endocarditis, enteric fever, malaria

and miliary tuberculosis, which were the possibilities considered during the first week of hospitalization. The correct diagnosis was not made until the previous symptoms of an ill defined abdominal episode involving the bowel were taken into account. In contradistinction to this case, the majority of the reports in the literature deal with cases in which the syndrome developed under direct observation after the removal of an inflamed appendix or gall bladder. As noted above, the bacteriologic findings in the portal system, liver and blood mirrored the pathogenic flora usually found at the site of the initiating suppurative process.

The chronologic history of the treatment of this condition can be divided into two eras: surgical therapy, consisting of ligation of the involved veins or appropriate drainage of liver abscesses and other suppurative foci or both[4-7]; and the addition of antibacterial therapy to the attack.[8-12] In Soro's[3] survey of 68 cases of pylephlebitis 39 patients were operated upon, and 32 of these died; the remaining patients who were not operated on died. It is our impression, from a survey of the literature, that the use of antimicrobial agents has materially lowered the mortality in this disease. There are no published data to indicate the role of better surgical technic, safer anesthesia and more complete general supportive measures in attaining a higher recovery rate. Two of the case reports deal with recovery without surgical drainage or venous ligation.[10, 11]

The case reported above illustrates several points deserving emphasis. Adequate, specific and prompt antibacterial treatment is of definite value, and must be continued for at least seven to ten days into the afebrile stage. Surgical procedures may remain an integral part of the therapeutic program, and their efficacy may be enhanced by previous and continuing antimicrobial therapy. In cases of undiagnosed septicemia, a careful analysis of the preceding events, particularly those relating to abdominal complaints, may aid in making an early diagnosis of suppurative pylethrombophlebitis.

Summary

The clinical and laboratory features of a case of suppurative pylethrombophlebitis with liver abscess, which was apparently cured by an energetic combined medical and surgical attack, are presented. The literature pertaining to this entity is briefly reviewed, with special reference to the role of antibacterial agents in achieving recovery.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SCIENCE: BIOCHEMISTRY*

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THE first half of this century has seen a remarkable development in the science of biochemistry. This subject has emerged from its status in the last century as merely an occasional chapter in the field of physiology or of chemistry and from its designation, in a somewhat minor key, as "animal chemistry," "chemical physiology" or "physiologic chemistry." No longer is it hidden in the academic catalogue as a weak addendum to a course in physiology or in chemistry, but it has taken its place as a robust and integral subject in the curriculum of the college, the university and the medical school. Its investigative potentials have burst forth in an ever-widening circle of creativity and have realized themselves in a host of related fields. Hoppe-Seyler's *Zeitschrift für Physiologische Chemie*, first issued in Germany in 1877, and sufficient for the needs of that day, has been joined in this century and in other lands by the *Journal of Biological Chemistry* (United States, 1905), the *Biochemical Journal* (Britain, 1906), *Biochemische Zeitschrift* (Germany, 1906), the *Journal of Biochemistry* (Japan 1922), *Bulletin de la Société de Chimie Biologique* (France, 1914), *Biokhimichnii Zhurnal* (Russia, 1926), *Archives of Biochemistry* (United States, 1942), *Annals of Biochemistry and Experimental Medicine* (India, 1941), *Annual Review of Biochemistry* (United States, 1932) and *Biochimica and Biophysica Acta* (International, 1947).

It may be well to recognize that to some degree the advances in biochemistry have merely been part of the broad and rapid sweep of science that has characterized the nineteenth and twentieth centuries. In addition, closer consideration will show that progress in biochemistry has had a highly specific effect on other fields. As biochemistry has developed, the workers in all biologic sciences — botanist, zoologist, agriculturist and physicians in all branches of preclinical and clinical medicine — have been forced to re-examine their ideas in terms of newer biochemical formulations. One need only leaf through the pages of such periodicals as the *American Journal of Botany*, the *Anatomical Record*, the *Journal of Pharmacology* or any of a number of clinical journals for the past twenty-five years to appreciate vividly how biochemistry has come to play an increasingly insistent role in these various disciplines.

The question arises whether twentieth-century biochemistry possesses any characteristics that are relatively unique and so tend to distinguish it from that of the last century. Although it is tempting at first sight to conclude that the biochemistry of the nineteenth century was mainly descriptive whereas that of the twentieth is dynamic, historical considerations do not appear to support this distinction. The dynamistic aspects of biochemistry

FIGURE 1. *Dr. John J. Abel (1857-1938), Pioneer in Isolation of Hormones and Prime Mover in the Founding of the American Society of Biological Chemists in 1906 (Photograph by Courtesy of Dr. E. M. K. Geiling).*

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were of much interest even in the nineteenth century. As long ago as 1803, W. B. Johnson, in his *History of the Progress and Present State of Animal Chemistry*, stated: "Modern chemistry has already thrown great light on several parts of the animal system; it has within these last few years commenced an investigation of several of the functions of the body, and explained the manner in which they are carried on with some degree of success." In his preface to the first volume of his textbook of the physiologic chemistry of the animal body (1880), Gamgee showed himself as aware of the necessity of discussing the chemical processes relating to the elementary tissues of the body as of describing their chemical composition.

Nor is this interest in dynamism in biochemistry at the beginning of the nineteenth century so curious in the light of certain general considerations. In an unusually interesting and stimulating essay entitled "The Place of Science in Modern Civilization," written in 1906, Thorstein Veblen presented the idea that the cultural structure of the day is reflected in scientific procedure and formulation. Thus, the era of the hand artisan was paralleled in science by concern with descriptive material and concepts of discrete cause and effect, whereas the Industrial Revolution and the introduction and use of the machine in the late eighteenth and early nineteenth centuries were accompanied in scientific thought by a pattern that "constructs the life-history of a process in which the distinction between cause and effect need scarcely be observed in an itemized and specific way, but in which the run of causation unfolds itself in an unbroken sequence of cumulative change."

The scientific formulations of the twentieth century have become a matter of the perception of the more intricate, detailed and delicately adjusted features of the "sequence of cumulative change" in a natural phenomenon. Accordingly, the distinctive character of biochemistry in this century may be considered to lie in the accumulation of descriptive material in increasingly finer detail, and the amazing acceleration in perceiving the more intricate dynamic relations that this accumulation has made possible. For example, the German biochemists of the latter half of the nineteenth century who were interested in metabolism were imbued with the idea that the animal organism was a machine that was capable of converting the potential energy of food into heat energy and work, and they were concerned in determining the over-all aspects of this conversion. But it was descriptive investigation of the structure of carbohydrates and phosphorylated compounds, the demonstration of enzyme activity independent of cellular organization and the characterization and isolation of such enzymes that permitted the elucidation of the finer details in the chain of processes involved in the transformation of this energy in the animal organism.

It is manifestly impossible, in this brief essay, to consider in any comprehensive and detailed manner the advances in biochemistry during the first half of this century. These may be broadly listed as follows: the elucidation of the finer details of the chemical structures of the major cell compounds — namely, the proteins, carbohydrates and lipids; the elucidation of the structure of specialized substances of the organism such as hemoglobin, porphyrins, bile acids and various pigments; the discovery of the role of the accessory food factors or vitamins, their isolation and chemical identification, and the demonstration of their role in certain metabolic reactions; the study of enzymes, with respect to both their kinetic characteristics and the particular metabolic reactions that they catalyzed, the characterization of enzymes as chemical substances and their isolation in pure form; the isolation and chemical characterization of the hormones and related substances and the demonstration and definition of their role in directing metabolic reactions; the development of biochemical technology and methodology; and the applications of these advances to a study of biologic processes and, more particularly, to human medicine.

Major Cell Components

By the end of the nineteenth century, investigations into the chemical nature of proteins had established several important facts. A number of proteins, such as the globulins of hemp seed and castor-oil seed, albumin from hen's egg and hemoglobin, had been crystallized. Intensive analytical work had established the elementary composition of these and other proteins and had indicated the extraordinary size and complexity of the protein molecule, but had failed to establish fine distinctions between them. Johnson's prediction in 1803 that new methods such as the use of acid, alkali and alcohol in place of open distillation would be useful in unraveling the structure of proteins had realized itself by the end of the nineteenth century in the isolation of thirteen amino acids. A scheme of protein classification, based partly on solubility and partly on combination with other organic groups, had been in force for some time.

It was early in this century, in 1906, that Emil Fischer presented a comprehensive plan for the study of protein structure. Among the tasks he outlined and later fulfilled in large measure were to prove the structure of amino acids, isolable from proteins, by synthesis, to find chemical derivatives that could facilitate the separation of mixtures of amino acids and to study the manner in which amino acids were combined with each other in peptides and polypeptides. Knowledge of protein chemistry was also advanced by Kossel's work on the basic amino-acid-containing proteins, by the continuing isolation of amino acids and by the amino acid analyses of various proteins. But the beginning of the

twentieth century also saw the application of a new approach — namely, the physicochemical — in the investigation of protein structure and characteristics. This approach was to prove extraordinarily fruitful and to yield much valuable information concerning the molecular weights of various proteins, the existence of various reactive groups on the protein molecules, the quantitative aspects of the interaction of these groups with acids, bases, metal ions, dyes and other compounds, and the molecular configuration of proteins as revealed by electron microscopy and x-ray analysis.

As compared with other fields, that of lipid biochemistry was relatively inactive during the first quarter of this century. In 1924 Armstrong, in an address entitled, "A Neglected Chapter in Chemistry: the Fats," stated, "This account of our knowledge of the fats and some of the many problems needing study, particularly in the organic branch of chemistry, is mainly written with the hope of reviving interest in them as, apart from physical and analytical investigations, no other province of chemistry has been so little studied in recent years." The second quarter of the century saw an intensive spurt in the descriptive aspects of this branch of biochemistry. A number of excellent and detailed monographs that have appeared within the past few years attest fully to the products of this revived interest. One need only compare Hilditch's recent edition of *The Chemical Constitution of Natural Fats* with the Ulzer revision, in 1903, of Benedikt's volume *Analyse der Fette und Wächsarten*" to realize the enormous strides that have been made in knowledge of the structure of lipids. Thus, during the past two decades there has been a marked acceleration in the study of the structure of natural fats of a wide variety of species from the animal and plant kingdoms. The nature and distribution of fatty acids in the triglyceride molecule have become a major concern, and statistical considerations have been invoked to aid in the elucidation of these structures. Conjugated lipids, such as the phospholipids and cerebrosides, that are of physiologic interest have been subjected to increasingly finer analysis, and the distribution of these compounds in tissues has been studied intensively. Interest has also arisen in a relatively new class of compounds, the lipoproteins.

Although, as indicated above, concern with the structure of the lipids lagged during the first quarter of this century, interest in the mechanisms of fat metabolism proceeded apace. Indeed, little about this field was known prior to this century; in 1904 Knoop ingeniously introduced the use of the phenyl derivatives of the lower fatty acids to trace their metabolism and, as a result of these studies, formulated the concept of beta oxidation. Subsequent investigations sought to refine and modify this concept. Another considerable forward step in this field occurred when Schoenheimer and Rittenberg introduced the use of deuterium-labeled compounds. The information that this and other tracer technics contributed to knowledge of the synthesis of fats, their intermediary metabolism and their conversion to other cell components is, of course, too complex to be detailed here.

The titanic efforts and accomplishments of Emil Fischer made themselves also felt in carbohydrate chemistry, and his labors in this field bridged the nineteenth and twentieth centuries. When he began his work in carbohydrates in 1886, the only three hexoses known were D-glucose, D-fructose, and D-galactose. His introduction and use of phenylhydrazine and his application of what were then new concepts of stereochemistry proved to be extremely fruitful. When Emil Fischer died in 1919, fourteen out of the sixteen possible aldohexoses had been prepared and characterized; twelve of these were due to the labors of his group.

The first half of this century has been marked by an intensification in the study of the structures of the monosaccharides and higher saccharides and their derivatives. The names of Armstrong, Hudson, Irvine, Hirst and Haworth are outstanding in the list of accomplishments. The concept of a ring structure, proposed by the biochemists of the late nineteenth century, was clarified and defined more precisely by the American and British workers and culminated in Haworth's pyranose formula. During the past twenty-five years, the structure and properties of the polysaccharides such as glycogen, starch, cellulose, inulin and the polymers of galacturonic acid, mannose and various pentoses have become the focus of attention.

Advances in the field of carbohydrate metabolism have been no less impressive. Indeed, ideas in this area have been formulated and revised anew several times. The over-all reversible reaction, glucose $\rightleftarrows$ glycogen, has been resolved into a series of three reactions catalyzed by the enzymes, hexokinase, phosphoglucomutase and phosphorylase. The anaerobic phase of carbohydrate metabolism — namely, the conversion of glycogen to lactic acid — and the aerobic phase, or the oxidation of pyruvic acid, have similarly been resolved into series of enzymatic steps. The names of Warburg, Meyerhof, Embden, Parnas, Krebs and the Coris loom large in the development of this aspect of biochemistry.

Specialized Products of the Plant and Animal Organism

Advances in this field offer a good illustration of the thesis that the biochemists of the present century have been just as interested in the descriptive as in the dynamic aspects of their subject, and that the development of the latter is dependent upon information supplied by the former. The specialized products of the plant and animal organism referred to are of considerable physiologic importance, and a knowledge of their chemical structures is essential

to a fuller understanding of the roles that they play in metabolism.

The landmarks in this area of biochemical progress are Wilstätter's studies on vegetable dyestuffs and chlorophyll, the work of Wieland and of Rosenheim and King in unraveling the structure of the bile acids, Windaus's success in elucidating the structures of the digitalis glycosides, cholesterol and other sterols, and Hans Fischer's work on the constitution of the porphyrins and the synthesis of hemin.

It may be of interest to recount the development of knowledge of bile acid and cholesterol chemistry in order to illustrate the manner in which twentieth-century biochemistry has brought technics of increasing refinement to bear upon the details of an inherently difficult problem. By the beginning of the twentieth century, little but the empirical formula and the presence of a hydroxyl and a double bond was known concerning the structure of cholesterol. These findings indicated that cholesterol contained four rings. Similar inferences were drawn about the bile acid structure. It was in the first part of the twentieth century that investigation concerned with the examination of the products of oxidation was inaugurated; Windaus's work on cholesterol began in 1903, and Wieland initiated his study of bile acids in 1912. Work on the characterization of the four carbocyclic rings and the side chain progressed until 1928, when it was considered that the formulas of cholesterol and bile acids had been definitely established, and the award of the Nobel Prize of that year to Wieland and Windaus was a fitting recognition of their prodigious labors.

The Wieland–Windaus formulas represented three rings meeting at one point. Several years later, in 1932, Bernal noted that the x-ray crystallographic examination of ergosterol and its irradiation products did not support the Wieland–Windaus concept of a thick molecule, but was in favor of a long, thin molecule. As a result of these observations, Rosenheim and King considered the possibility that chrysene, which was known to result from the heating of bile acids or cholesterol with selenium, was not the product of a drastic rearrangement of these structures but rather a normal degradation product. Accordingly, they assumed that the four rings of cholesterol and the bile acids were in chrysene-like apposition. The agreement of this formula with x-ray data and with other chemical data proved satisfactory.

Discovery of the Vitamins

The discovery of the role of accessory food factors, or vitamins, and their isolation and chemical identification is a biochemical triumph that has taken place almost wholly within the present century. Although there were dim and even mystical surmises during the sixteenth and seventeenth centuries and in ancient times that certain foods were necessary to prevent what are now known to be deficiency diseases, these ideas did not approach clarity until the latter half of the nineteenth century. The close of the century was marked by two observations that are now classic. In 1887 Takaki observed that increasing the content of meat, vegetables and condensed milk in the diet of the Japanese sailor greatly decreased the incidence of beriberi. In 1897 Eijkman produced beriberi in hens by the feeding of milled rice and prevented this condition by the addition of rice bran.

But it was not until the beginning of this century that the theory of essential accessory food factors was definitely formulated. In 1906, Hopkins wrote:

> But further, no animal can live upon a mixture of pure protein, fat and carbohydrate, and even when the necessary inorganic material is carefully supplied, the animal still cannot flourish. The animal body is adjusted to live either upon plant tissues or other animals, and these contain countless substances other than the proteins, carbohydrates and fats. . . The field is almost unexplored, only it is certain that there are many minor factors in all diets, of which the body takes account. . . Scurvy and rickets are conditions so severe that they force themselves upon our attention, but many other nutritive errors affect the health of individuals to a degree most important to themselves, and some of them depend upon unsuspected dietetic factors.

This statement and the experimental work upon which it was based were the heralds of impressive developments that, within a period of thirty years, were to culminate in the isolation and identification of these "unsuspected dietetic factors." Only a few examples can be cited to illustrate this laborious, sometimes tortuous, but on the whole inevitable course of investigation. In 1909 Hopkins, in England, discovered that certain fat-soluble substances were necessary for the growth of mice and rats. In the United States McCollum, in 1915, found that the growth factor was present in cod-liver oil and in butter, and termed it vitamin A. The constitution of carotene was established in 1930, and its conversion to vitamin A was demonstrated soon thereafter. The next year Karrer obtained a highly potent vitamin A preparation and determined its structure. The synthesis of vitamin A was announced by Kuhn and Morris in 1937, and the vitamin was soon available in crystalline form.

The identification of the other vitamins has followed a similarly dramatic course. In 1926 Jansen and Donath prepared crystalline thiamine from rice bran, and in 1931 Windaus and his co-workers established its empirical formula. The chemical structure was elucidated by Williams in 1936, and its synthesis was accomplished later in the year. In 1928 Szent-Györgyi isolated a hexuronic acid from adrenal glands, oranges and other substances; its identity with vitamin C or the antiscorbutic factor was established by several groups of workers in 1932. In the next year its constitution was determined, and its synthesis accomplished.

The course of discovery of vitamin D was particularly exciting. In 1919 Mellanby found that a fat-soluble factor was capable of curing rickets in dogs, and in the same year Huldschinsky observed that ultraviolet light was capable of curing rickets in infants. Three years later Zucker and his associates found that the antirachitic factor was present in the unsaponifiable fraction of fish-liver oil, and McCollum determined that the fat-soluble vitamin A and the antirachitic factor were two distinct substances. A relation between the curative properties of ultraviolet light and the as yet unknown antirachitic factor became apparent in 1924, when Steenbock and his associates and, independently, Hess and his co-workers found that antirachitic potency could be induced in foods by ultraviolet radiation. In the next year it was established that this induction was due to irradiation of the sterol fraction in foods. The search narrowed, and, within a few years, the essential component in this fraction was found to be ergosterol. In 1931 Reerink and van Wijk isolated for the first time a crystallized vitamin D preparation resulting from the activation of ergosterol. It was soon recognized that several closely chemically related substances possessed antirachitic activity. In 1935 Windaus and his associates synthesized the natural provitamin D, 7-dehydrocholesterol, and two years later Schenk obtained the crystallized vitamin D_3 by activation of this provitamin.

Equally fascinating as those described were the discovery and identification of the many other vitamins that have now become familiar; riboflavin, pyridoxin, nicotinide and nicotic acid, pantothenic acid, inositol, para-aminobenzoic acid, the group of tocopherols or vitamins E, biotin, the group of vitamins K and a whole group of other vitamins falling into the vitamin B complex class. Only within the past few years has this area of investigation reached a new climax with the isolation of vitamin B_{12}, the antipernicious-anemia factor.

Enzymes

The subject of enzyme action or, as it was more broadly termed, fermentation received considerable attention during the nineteenth century. Several crude enzyme preparations were obtained. Berzelius and von Liebig propounded a purely chemical, nonvitalistic theory of enzyme action according to which an enzyme was an "albuminoid" in the act of decomposing and hence capable of imparting this property of decomposition to other materials. The discoveries of Pasteur, epochal as they were in revealing the existence and details of the microbiologic world, retarded the chemical theory of enzyme action. "The chemical act of fermentation," wrote Pasteur, "is essentially a correlative phenomenon of a vital act beginning and ending with it." Thus, toward the close of the nineteenth century the idea was widely prevalent that enzyme activity was dependent upon the presence of cellular structure or, at the very least, upon some kind of residue of a vital force from the living cell.

These neo-vitalistic concepts became outmoded as the result of three outstanding series of investigations begun during the last years of the nineteenth century and the early years of the twentieth. The first of these was the inauguration by O'Sullivan and Thompson of quantitative studies on the course of enzyme action; although their conclusion that invertase action followed a monomolecular course has been subsequently disproved, their approach stimulated many other kinetic enzyme studies. The second achievement was the work of Emil Fischer and his colleagues on the specificity of enzyme action. The "lock and key" simile, first devised by Fischer to explain the activity of an enzyme in terms of the ease of spatial combination with its substrates again tended to emphasize the chemical nature of enzyme action. But the most convincing denial of the neo-vitalistic concepts of enzyme action was Buchner's discovery, in 1897, that a cell-free yeast extract was capable of causing alcoholic fermentation.

Stimulated by these initial studies and discoveries, enzyme investigation has expanded so greatly during the first half of this century that it has come to assume an increasingly basic and commanding role in biochemistry. During the first quarter of the century, the chief emphasis lay in defining the conditions, such as pH, temperature, substrate and enzyme concentration, that influenced enzyme action, and in this way attempting to arrive at a mathematical formulation of the kinetics that would give an insight into the nature of enzyme action. Sörensen's demonstration, in 1909, that enzyme activity was dependent upon pH removed a factor that produced variation and uncertainty in the determinations of enzyme activity, and proved to be a prerequisite for all subsequent enzyme investigations. The next important development was made by Michaelis and Menten, who found that the reaction velocity was proportional to the concentration of an assumed intermediate enzyme-substrate complex in accordance with mass law requirements in a homogeneous system. The third major advance during the first twenty-five years of this century was the recognition that enzymes were involved in oxidative as well as hydrolytic reactions. Battelli and Stern, Bach and Chodat began the systematic study of oxidases. Thunberg's invention of the methylene blue technic facilitated the study of many of the oxidizing-reducing enzymes, and Warburg inaugurated his investigations on the oxygen consumption of tissues.

During the past twenty-five years, the major preoccupations of workers in this field have been the isolation of enzymes in purified or crystallized form, and the elucidation of the role that these enzymes played in cellular metabolic reactions.

This phase was ushered in by the preparation of crystalline urease by Sumner in 1926. In 1930 Northrop isolated pepsin in crystalline form, and in 1932 he and Kunitz crystallized trypsin. By 1946 twenty-nine enzymes had been isolated in this form, and each year sees the addition of others to the list.

The crystallization of enzymes has made possible the study of their properties in much the same manner as other proteins are being studied. Of particular interest is the observation that in a certain number of enzymes the activity is dependent upon the combination of a specific protein with a prosthetic group, which is frequently a vitamin. Some of the better known prosthetic groups are the cocarboxylase of carboxylase, adenylic acid of animal phosphorylase, the diphosphopyridine and triphosphopyridine nucleotide components of several dehydrogenases, riboflavin phosphate of the old yellow enzyme, isoalloxazine-adenine dinucleotide of d-amino acid oxidase and pyridoxal phosphate of transaminase. As we have already noted, the purification and isolation of enzymes have also been of substantial aid in unraveling the detailed sequence of reactions in metabolic processes.

Hormones

By the beginning of this century, the importance of most of the organs of internal secretion had been fairly well indicated as a result of the observations of Addison, Gull, von Mering and Minkowski, and Marie. Moreover, through the work of Claude Bernard, Brown-Séquard and Gley, the concept had developed that various organs were capable of delivering substances that they formed directly into the blood. In the Croonian lecture of 1905, Starling suggested that the term "hormones," from the Greek meaning "I excite," be employed to designate chemical substances that, secreted by a specific tissue into the blood, could arouse distant tissues to activity. However, practically nothing was known about the chemical nature and biochemical actions of these secretions. The development of these areas of knowledge has taken place wholly within this century.

The identification of some of the hormones may be briefly recounted. The isolation of epinephrine, the hormone of the adrenal medulla, was accomplished by Abel at the very beginning of the century, during the years 1898-1902. The chemical structure was elucidated within the next few years, and the compound synthesized by Stolz in 1904. The next hormone to be isolated was that of the thyroid gland by Kendall in 1915. The chemical constitution of thyroxin was determined by Harington in 1926, and its synthesis accomplished by Harington and Barker in the next year. The story of the discovery and isolation of insulin is now a classic in the annals of medicine. The general effect of this hormone had been recognized for thirty years before active and therapeutically effective extracts were obtained by Banting and Best in 1922. The protein nature of this hormone was soon demonstrated, and its preparation in crystalline form achieved.

Of equally compelling interest were the advances in the field of sex hormones. Limitation of space prevents a description in detail of the progress of events that led from the observation by Allen and Doisy in 1923 that follicular fluid contained an estrogenic substance to the isolation of the crystalline hormone, estrone, in 1929. The isolation of the male hormone, androsterone, from urine was accomplished by Butenandt in 1931. Within the next few years, other sex hormones, dehydroisoandrosterone, testosterone and progesterone were obtained, and their structures were determined.

The discovery, shortly before 1930, that adrenocortical extracts could prolong the life of adrenalectomized animals stimulated the study of the steroids present in the adrenal cortex. By 1949 nearly thirty crystalline substances had been isolated. Although the functions of these compounds have not been fully explored, it has been found that a number, like 17-hydroxycorticosterone and 17-hydroxy-11-dehydrocorticosterone, are active in controlling carbohydrate and protein metabolism in the liver and muscle whereas others, of which desoxycorticosterone is the most potent, regulate sodium metabolism.

That the pituitary body appears to exert a considerable variety of hormonal influences was recognized early in this century. In 1928 two fractions were separated from the posterior pituitary body; one had marked oxytocic activity, and the other was strongly vasopressor and antidiuretic. It was, however, the anterior portion of the pituitary body that exerted most of the hormonal actions, and the task of unraveling these has been marked by painstaking labor and brilliant inspiration. There is definite evidence today for the existence of six anterior pituitary hormones and ample indications for a number of others. The isolation of the growth and adrenocorticotrophic hormones has been a particularly outstanding accomplishment. The latter hormone has permitted a more precise investigation of the relations between the anterior pituitary body and the adrenal cortex, and the manifold physiologic and biochemical processes that are under the control of these glands. The therapeutic triumph achieved by use of adrenocorticotrophic and 17-hydroxy-11-dehydrocorticosterone (Cortisone) in the treatment of rheumatoid arthritis is well known, and the stimulus that this has given to the study of the mechanisms involved in other diseases has been considerable.

Biochemical Technology and Methodology

Many of the advances described above would not have been possible without comparable ad-

vances in apparatus, methods and technic. Of the new types of apparatus, the following may be mentioned: the ultracentrifuge, the electrophoretic apparatus, the countercurrent distribution apparatus, the Warburg tissue respiration apparatus and its subsequent modifications, the Van Slyke volumetric and manometric apparatuses and spectrophotometers with ranges in the ultraviolet and infrared as well as in the visible region. The elaboration of chromatographic technics and the development of a great array of micro and ultramicro analytical methods have been of invaluable aid in the analysis of biochemical components from the tissues and body fluids and in determining the chemical nature of many of these compounds. Probably the outstanding technical biochemical advance in this century has been the introduction of the isotopic methods. These have been applied to the determination of the amount of a constituent in a mixture and to the measurement of rates of reaction, but chiefly to tracing the pathways of intermediary metabolism.

FIGURE 2. *Emil Fischer (1852-1919) in His Berlin Laboratory in 1904 at the Age of Fifty-Two (Photograph by Courtesy of Dr. H. O. L. Fischer).*

APPLICATIONS OF BIOCHEMISTRY

As pointed out above, the biochemical advances of this century have inpinged upon many related sciences. To an increasing extent, the workers in these sciences have availed themselves of these advances as another channel, and quite often a more fundamental one, through which they might further explore their own fields of interest. Genetics, bacteriology, botany, immunology, pharmacology and clinical medicine are some of the fields in which these biochemical aspects have begun to assume a substantial role within recent years.

It may be of interest to illustrate the nature of these biochemical applications in somewhat greater detail in one of these fields — namely, medicine. By the end of the last century, the segment of biochemistry that concerned itself with human disease had evolved some qualitative tests for abnormal urinary components and some crude methods for determining gastric function. The blood had been analyzed for some of its components, but the procedures employed were laborious and required large amounts of blood.

The development of easily executed, quantitative methods for the determination of blood and urinary biochemical components is distinctly an achievement of the present century. Indeed, it was not until the second decade that methods of this kind began to appear — for example, Bang's micro copper reduction method and Lewis and Benedict's picrate method for blood sugar. In 1919 Folin and Wu submitted a compact system of blood analysis that permitted the measurement of sugar, urea and other components in the same tungstic acid filtrate of blood. Gasometric methods for analysis, introduced by Haldane and Barcroft at the turn of the century, were greatly simplified and their applications extended by Van Slyke and his group. It was

FIGURE 3. *The Countercurrent Distribution Apparatus, One of the Recent Advances in Technic for the Separation of Substances of Biochemical Interest (Photograph by Courtesy of Dr. L. C. Craig).*

also during the second decade of this century that venipuncture became an accepted procedure and thus made blood from large numbers of patients readily available for analysis. One of the major applications of biochemistry since 1915 has been the elucidation of the relation between various pathologic processes and alterations in the concentration of blood chemical components. The building of this stock of information has helped not only in the diagnosis of these various diseases but also in the understanding of their underlying mechanisms.

The application of the blood analytical methods to the products of fecal and urinary excretions facilitated the institution of metabolic-balance experiments and added another dimension to the study of the biochemical aspects of disease. The great variety of mechanisms thus revealed and elucidated may be indicated by the following brief list: calcium and phosphorus metabolism in hyperparathyroidism, hypoparathyroidism and various bone diseases; the excessive excretion of electrolytes in diabetic acidosis; the development of acidosis in infantile diarrhea; fat and mineral absorption in the steatorrheas; hypopotassemia in diabetic acidosis and postoperative states; and the influence of adrenocorticotrophic hormone and the adrenal steroids on nitrogen and mineral metabolism.

Other fields of medicine have availed themselves of the biochemical advances of this century. Thus, in nutrition, studies of blood concentrations and urinary excretions of vitamins at varying levels of intake have given a deeper insight into the evolution of the avitaminoses and the normal vitamin requirements. Understanding of such disorders as the lipoidoses, gout, hemochromatosis and the inborn errors of metabolism has been illumined greatly by the application of biochemical principles. Endocrinology, once an easy prey to obscurantism, has been set upon a sound biochemical and physiologic basis. The list could continue almost indefinitely. It may be said, in summary, that no field of medicine, from surgery to psychiatry, has been exempt from the impress of the biochemical advances that have occurred during the first fifty years of this century.

The Past and the Next Fifty Years

It is difficult to complete a survey of the advances in biochemistry during the past fifty years without asking what the next half century will bring. The answer must admittedly be vague and indefinite. However, since the pace of science has not only increased but has constantly accelerated, it may be predicted that, barring a cultural cataclysm, great as the biochemical advances have been during the past fifty years, they will easily be surpassed by those of the half century to come.

If one tries to imagine the kind of basic biochemical discoveries the next half century will bring, the only guide is the knowledge that the last fifty years saw the emergence of such fields as vitamins, enzymes and hormones, the existence and potentialities of which were unknown or were but vaguely realized before 1900. Yet these fields have furnished major concepts for understanding the common bases for several groups of biochemical processes. One may predict that the next fifty years will similarly see the emergence of other great unifying ideas, at present but dimly conceived. Perhaps one of these will deal, as Szent-Györgyi has recently noted, with the application of quantum mechanics and the theory of the solid state to protein molecules. Perhaps another concept will be concerned with the integration of the various inhibitory and accelerative effects on enzyme activity in the continuum of the cell. Or perhaps the next fifty years will see the discovery of a class of substances or physical agents present within the body that fundamentally influence metabolic activities but whose existence today is totally unsuspected.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 37021

PRESENTATION OF CASE

First admission. A sixty-eight-year-old man was admitted to the hospital because of back pain.

Three months prior to admission he noted the insidious onset of anorexia and easy fatigability associated with dull pain in the right lumbar region. He was treated conservatively, but the symptoms increased and he developed pallor, lost 25 pounds in weight, appeared mildly cachectic and had a heart murmur. A blood culture showed alpha-hemolytic streptococci and immediately thereafter he was referred to the hospital.

The patient had diphtheria and malaria in the past, but there was no history of rheumatic fever or hypertension.

On physical examination there were no petechiae. The lungs were clear and the heart was not enlarged. There was a faint aortic diastolic murmur. The liver and spleen were questionably palpable.

The temperature was 98°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 60 diastolic.

Examination of the blood revealed a hemoglobin of 12.8 gm., and a white-cell count of 7800, with 72 per cent neutrophils. The sedimentation rate was 32 mm. in one hour. A stool was normal. A blood culture was positive for alpha-hemolytic streptococci. X-ray films of the chest showed the lungs to be clear. The heart was enlarged in the region of the left ventricle. The aorta was calcified, tortuous and dilated in the ascending portion. The pulsations were increased, and there was a rapid diastolic return suggesting aortic regurgitation.

The patient was treated with large dosages of penicillin intravenously and intramuscularly, and the blood culture promptly became negative. He was practically afebrile throughout the illness, and he was discharged symptom free after one month. The murmur had not changed.

Final admission (eleven months later). He remained in good health for a period of four months and gained about 25 pounds. He then experienced a severe paroxysm of nocturnal dyspnea that during the ensuing three months recurred once every three or four weeks. Gradually, the attacks increased in frequency until they occurred three or four times weekly. He was digitalized, put on a low-salt diet and treated with ammonium chloride, mercurial diuretics and elevation of the head of the bed, without marked or sustained improvement. Two months later he began to have considerable exertional dyspnea and severe substernal discomfort both on exertion and at rest. He began to lose strength and lost 25 pounds in weight in several months. Auricular fibrillation was noted six weeks prior to admission. He remained consistently afebrile, and several sedimentation rates were in the range of 4 mm. per hour. Several blood cultures were negative. The white-cell counts and hemoglobin remained normal. Approximately four weeks before admission dyspnea, orthopnea, angina pectoris and palpitation increased markedly, and he noted vague generalized abdominal discomfort. The liver and spleen became definitely palpable one week before admission.

On physical examination the neck veins were distended and pulsating. A few fine rales were heard at both lung bases. The heart was enlarged to the left, and the rhythm was totally irregular, with a rate of 104 at the apex. High-pitched diastolic and soft systolic murmurs were heard all over the precordium. A diastolic rumble was heard at the apex. The liver was palpable two fingerbreadths below the right costal margin. The spleen was palpable two fingerbreadths below the left costal margin. There was no clubbing of the digits or peripheral edema. No petechiae were found.

The temperature was 98.4°F., the pulse 90, and the respirations 25. The blood pressure was 110 systolic, 65 diastolic.

Repeated urinalyses revealed a specific gravity ranging from 1.018 to 1.012 and a constant albuminuria, the tests varying from + to ++. The sediment contained rare to 3 red cells and 1 to 15 white cells per high-power field and occasional hyaline and rare granular casts. Examination of the blood disclosed a hemoglobin of 14.5 gm., and white-cell counts varying from 13,700 to 21,600, with 88 to 95 per cent neutrophils. The sedimentation rates were 3 to 8 mm. in one hour. The stools were guaiac negative on six occasions. The vital capacity was 66 per cent. A blood culture was sterile on admission.

The patient was placed on strict bed rest with salt restriction. The digitalis dosage was increased,

and mercurial diuretics were given at intervals of one or two weeks. Paroxysms of substernal oppression and discomfort were frequently recurrent but always relieved by nitroglycerin tablets. An electrocardiogram on the second day showed auricular fibrillation at an average rate of 90. The T waves were upright in Leads 2, 3, V_1, V_2, V_3 and V_4, and inverted in Leads 1, V_5 and V_6. The ST segments were sagging in Leads 2, V_5 and V_6.

Initially, the heart rate slowed, the dyspnea diminished, the pulmonary rales disappeared, and the liver and spleen were no longer palpable. He became ambulatory. He complained occasionally of vague discomfort in the right lower chest. On the thirteenth hospital day he had a severe attack of substernal pain and oppression, with radiation into the right lower chest unrelieved by nitroglycerin. He looked grave, anxious and sweaty, but no other significant alterations in physical findings were detected. There was no calf tenderness, and Homans's sign was negative. From this time on, the course was that of steady deterioration. An electrocardiogram on the following day showed no significant change from the previous one. In general the patient became more dyspneic and appeared weaker. He developed a moderately severe cough productive of white phlegm occasionally tinged with blood. On the sixteenth hospital day moderate oliguria was noted. The nonprotein nitrogen was 72 mg. per 100 cc., and the chloride 97 milliequiv., and the sodium 138.7 milliequiv. per liter. At this time he was described as cyanotic and breathless, with occasional Cheyne–Stokes respiration. The apical diastolic rumble was more pronounced, and the liver was again palpable. On the eighteenth hospital day one blood culture of four taken at hourly intervals was positive for *Streptococcus viridans*, but the plate was contaminated with *Proteus vulgaris* and isolation could not be performed. The patient was treated immediately with large doses of aureomycin and penicillin. Oxygen by mask was poorly tolerated and failed to relieve the dyspnea. With morphine sedation and an oxygen tent there was moderate improvement on the twenty-first and twenty-second hospital days, with disappearance of stupor and dyspnea and improvement in color and urinary output. The cardiac rhythm had now become irregular. On the twenty-third day his condition rather suddenly became worse, and he coughed up a teaspoonful of blood. A surgical consultant found slight enlargement of the right leg, with prominence of the superficial veins. Bilateral ligation and section of the common femoral veins were performed under local anesthesia, and a large thrombus was evacuated from the right femoral vein. The left was free of thrombus. The patient failed to improve and died nine hours later on the twenty-fourth hospital day.

Differential Diagnosis

Dr. David D. Rutstein*: There is no report of a blood Hinton test on this patient with an aortic diastolic murmur.

Dr. Tracy B. Mallory: It was not recorded.

Dr. Rutstein: The following points in the record are noteworthy: It is striking that this patient, suffering from his first attack of congestive failure, did not improve after treatment with digitalis and a mercurial diuretic, and one might question whether such therapy was given in adequate dosage, particularly since he later improved in the hospital on the same kind of therapy.

It is unusual that the apical diastolic rumble was heard after the onset of fibrillation but not before, and from the record it is not clear whether the development of the rumble was related to the change in rhythm or whether it occurred as an isolated event.

Alpha-hemolytic streptococci were found in one of four blood cultures. This is difficult to interpret because this organism is a common contaminant, and yet in certain cases of subacute bacterial endocarditis the blood cultures may be positive intermittently. It appears that the members of the house staff were also confused by this finding because they went to the trouble of taking four successive blood cultures over a period of a few hours.

Two other findings deserve comment. The high white-cell count with the high percentage of neutrophils was surprising because this patient had no clinical evidence of fever or infection. The presence of up to 15 white cells and an occasional hyaline and rare granular cast in the urine may be explained on the basis of the congestive failure.

Are there any x-ray films?

Dr. Stanley M. Wyman: The films taken at the original admission show no intrinsic pulmonary disease. The heart is definitely prominent in the region of the left ventricle, and the aorta is quite tortuous, particularly in its ascending portion, which is well seen in the left anterior oblique projection. There is a small amount of calcification in the aorta but no significant calcification in the ascending portion. Fluoroscopically, as noted in the record, this portion of the aorta did seem to show very rapidly collapsing pulsation in keeping with aortic regurgitation. The second set of films, taken on the final admission, show the heart shadow to have increased greatly in size, and there is now considerable engorgement of the hilar and pulmonary vascular shadows, with a finely granular pattern to the central lung fields, raising the question of some degree of pulmonary edema. I do not believe any calcification was seen within the heart itself fluoroscopically, and I do not see any on the films.

*Professor of preventive medicine, Harvard Medical School; associate physician, Massachusetts General Hospital.

The film of the abdomen is not particularly contributory. The spleen may be enlarged.

DR. RUTSTEIN: The films give me a much different impression from the one I received on reading the history. This patient suffered from heart disease and was probably recovering from subacute bacterial endocarditis superimposed on a previous lesion. I am faced with two problems — the primary etiology or etiologies of the heart disease, and the nature of the final episode that changed the course of the disease. The differential diagnosis lies among arteriosclerosis, syphilis and rheumatic fever. Arteriosclerosis is less likely, and since in Boston aortic disease in old people is not usually ascribed to arteriosclerosis, the discussion will be limited to that of the syphilitic versus the rheumatic etiology.

The following facts favor the syphilitic etiology — the aortic murmur appeared alone first without a mitral murmur, the course was relatively rapidly downhill, and the patient had evidence of aortic regurgitation and no evidence of aortic stenosis. Against this etiology is the episode of subacute bacterial endocarditis superimposed on an existing lesion and the development of auricular fibrillation.

The apical murmur may have been either a mitral diastolic murmur or an Austin-Flint murmur. The absence of a crescendo quality and its occurrence after the fibrillation in the presence of free aortic regurgitation suggest that it was an Austin-Flint murmur.

The patient rapidly developed signs of coronary insufficiency and angina pectoris, which might be ascribed to primary disease of the coronary arteries or to the aortic insufficiency with a lowered diastolic pressure. A diastolic pressure of 65 is just below the limits of normal, but in a patient who had a certain amount of coronary sclerosis, it might be significant as a cause of the anginal pain.

The final episode certainly was not characteristic of anything in particular. There was no evidence at that time of peripheral vascular disease, although it did occur later. There is no supportive evidence for myocardial infarction although the attack could be consistent with it. There was no history of hypertension and no physical or x-ray findings to suggest dissecting aneurysm. The question of mycotic aneurysm might be raised in a person who had subacute bacterial endocarditis, but again there was no particular evidence for that. A ball-valve thrombus or embolus in a coronary vessel in a patient who has had subacute bacterial endocarditis are some of the rare things one considers at a clinicopathological conference, but one does not pay much attention to these when one sees a patient. There was no good evidence for any of them.

I would conclude by making a diagnosis of old, healed subacute bacterial endocarditis, probably on the basis of old syphilitic heart disease, with probably some coronary sclerosis, multiple pulmonary infarctions and phlebothrombosis of the right leg.

DR. HOWARD B. SPRAGUE: We have discussed cases in these sessions in which the vegetations of the valves have been significant in producing many murmurs; for example, we have seen the murmur of mitral stenosis arising during subacute bacterial endocarditis due to vegetations on the mitral valve causing stenosis. As Dr. Rutstein says, we have also seen a simulated thrombus or popping up of vegetations in the aortic valve, a significant picture of a coronary obstruction. There was a sudden change in the picture with the development of dyspnea, which suggests that that may have been the explanation.

DR. WALTER BAUER: Why do you think the subacute bacterial endocarditis was healed?

DR. RUTSTEIN: Perhaps I should enlarge upon that. The temperature was normal, and the white-cell count was high, but the three blood cultures were negative.

DR. BAUER: I wondered if the episode the second time might just as well have been due to an active rheumatic myocarditis.

DR. RUTSTEIN: I think that is reasonable, but I could not be certain. The occurrence of rapidly progressive heart failure without response to mercurial diuretics or digitalis suggests its existence, but the subsequent course was not consistent with it. I believe that the left-sided failure was probably on a mechanical basis. Rheumatic myocarditis usually precipitates congestive heart failure, which is predominantly right sided.

DR. ARTHUR S. PIER, JR.: I was very much impressed with the great loss of weight and strength that this man had. It made me think that there was something else going on besides congestive failure that did not respond to any of the measures given. He did at first make a marked improvement in the hospital. The blood Hinton reaction was consistently negative. On his first admission the patient did have a transient aortic systolic murmur, but I thought that was probably due to dilatation of the aorta beyond the ring. There was a marked change in the character of the diastolic murmur between these two admissions. It was almost inaudible at first but became whistling and loud by the second admission. The spleen became palpable about a week before the second admission, which made me consider quite strongly the diagnosis of subacute bacterial endocarditis although I was never able to prove it. I thought the auricular fibrillation of recent onset was indicative of coronary-artery disease.

DR. BAUER: I do not see why this man did not have active subacute bacterial endocarditis at the time of his death, and that would explain the myocarditis very well.

DR. LEWIS W. KANE: Dr. Pier asked me to determine whether I thought this patient had active subacute bacterial endocarditis. I believed that he did not. I have never seen a patient relapse when the blood cultures were negative for three weeks after all therapy was discontinued. However, I suggested that hourly blood cultures be taken for four successive hours and that four plates be done. I have seen cases in which one or two out of four cultures are positive and the remainder negative. In this case one was positive for *Str. viridans*, but its significance was in doubt because the culture was contaminated by another organism.

CLINICAL DIAGNOSES

Subacute bacterial endocarditis.
Rheumatic heart disease.
Aortic regurgitation and auricular fibrillation.
Pulmonary infarction.
Bilateral femoral thrombophlebitis.

DR. RUTSTEIN'S DIAGNOSES

Healed subacute bacterial endocarditis on syphilitic aortitis.
Coronary sclerosis.
Multiple pulmonary infarctions.
Phlebothrombosis, right leg.

ANATOMICAL DIAGNOSES

Healed subacute bacterial endocarditis, mitral valve.
Rheumatic endocarditis, aortic valve, chronic.
Coronary arteriosclerosis, marked.
Myocardial infarction, left ventricle, recent massive.
Pulmonary embolism and infarction.
Phlebothrombosis, recent, femoral, bilateral.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy answered some of the questions but, as usual, not quite all of them. The primary disease was a rheumatic endocarditis of the aortic valve with a slight involvement of the mitral valve. The cusps of the aortic valve were definitely interadherent, which would not be seen in syphilis and is characteristic of an old rheumatic lesion. There was an ulcerated area on the surface of the mitral valve that appeared to be completely endothelialized, and we were inclined to believe that that was the focus of the bacterial endocarditis on the previous admission, which had completely healed. On the aortic valve was a fresh thrombus, 5 mm. in diameter, that microscopical examination showed to be composed purely of fibrin with some fibrinoid changes in the underlying valve substance. There was not a trace of inflammatory reaction of any sort nor signs of bacteria. It was indistinguishable from the terminal marantic thrombi that we see in cases of cancer, and it is hard to believe that this was actually a bacterial thrombus. The coronary arteries were markedly sclerotic, but we could find no point of thrombosis or occlusion. There was, however, a large infarct in the left ventricle on the left anterior surface of the septum. The lungs showed pulmonary infarction of both lower lobes, rather large ones, and thrombi were present in the corresponding arteries. The leg veins, as reported in the history, had been ligated, but fresh thrombi had formed both above and below the point of ligation on both sides so that there was the possibility of still further emboli if the patient had lived longer.

DR. BAUER: How often does this happen? I do not think that possibility is emphasized as often as it should be when ligation is advised.

DR. IRAD B. HARDY, JR.: I think it is very rare, Dr. Bauer.

DR. BAUER: Certainly, I have seen 4 or 5 cases.

DR. HARDY: We should like to ligate the veins a little earlier. This patient had hardly any circulation left when he was operated upon. The fact that thrombi were found at post-mortem examination certainly makes one wonder if ligation had helped this man, but I think this particular case, in which the patient was critically ill, does not illustrate what usually happens. I think the peripheral circulation was practically nil at the time the patient was operated upon. Can you say that they were antemortem thrombi?

DR. MALLORY: We believe that the thrombi were ante mortem. They seemed rather definitely adherent to the vessel walls. The aorta was tortuous, dilated and markedly sclerotic, but there was no evidence of syphilis.

DR. WYMAN: I should like to make one point on the calcification in the aorta: when there is no calcification of the ascending aorta, we consider it a point against syphilitic aortitis.

DR. PIER: Do you think the symptoms over the last months may have been due to repeated pulmonary infarcts, or did the infarcts all seem to be the same age?

DR. MALLORY: They all seemed to be the same age, which would have been a matter of five to seven days as near as I could estimate.

DR. JACOB LERMAN: No thrombi in the auricles?

DR. MALLORY: No.

A PHYSICIAN: Could you estimate the age of the myocardial infarction?

DR. MALLORY: That must have been present something over a week. Perhaps from one week to two weeks would be as close an estimate as I could give you on that.

CASE 37022

PRESENTATION OF CASE

A nineteen-year-old boy was admitted to the hospital because of a "bloated, distended abdomen and constipation."

The patient had had a protuberant abdomen as long as he could remember. In recent years this embarrassed him so much that he did not go swimming. Five years before entry he fell on his abdomen during a football game, following which he experienced severe, diffuse abdominal pain and cramps. In the course of the next few hours he voided "4 quarts" of urine, the pain subsided, and the abdomen became flat. The protuberance recurred in the course of a few weeks, but the patient remained well thereafter. Two days before admission the abdomen became more bloated than usual, and he had a mild abdominal ache, and was constipated.

With the exception of an episode of jaundice at the age of seven he had led a healthy and active life. There were no symptoms referable to the abdomen. His job of delivery boy entailed much climbing of stairs, but the patient never experienced any dyspnea, leg edema, weakness or fatigue. In the past he had had occasional abdominal cramps combined with slight constipation, but the bowels usually moved regularly once a day.

Physical examination was negative except for the abdomen, which was tense and protuberant. No masses were palpable, and peristalsis was normal. There was no shifting dullness, but a marked fluid wave was present over the entire abdomen. Tympany was present in the left flank. The entire abdomen was "sore," without a single point of tenderness.

The temperature, pulse and respirations were normal.

The urine was normal. Examination of the blood disclosed a hemoglobin of 11.5 gm. and a white-cell count of 6200. The blood chemical determinations were normal. Cultures of the urine and fluid aspirated from the abdomen were negative. A plain film of the abdomen showed diffuse increased density throughout and bulging both at the flanks and anteriorly. Because of the generalized haziness, it was impossible to differentiate abdominal viscera. Gas was scattered in the bowel without evidence of abnormal distention. An x-ray film of the chest was negative except for a small amount of fluid in the left costophrenic angle.

An abdominal tap produced thin, grossly bloody fluid. Following the tap the patient complained of more diffuse abdominal pain and pain in both shoulders. Cystoscopy and retrograde pyelography showed a normal bladder and normal right ureter and kidney except for some evidence of external pressure in the middle third of the ureter. The left ureter and lower calyxes were normal; the upper calyxes could not be filled. A urogram showed that the dye appeared promptly and in good concentration bilaterally. The left upper tract was not unusual except for a bifid renal pelvis. On the right there was moderate hydronephrosis and some distention of the right ureter down to the brim of the pelvis. The contour of the bladder was normal. On these films the lower border of the liver was not well made out, nor was the lower pole of the spleen identified with certainty although what was probably spleen was seen several centimeters below the costal margin. There was a ground-glass density to the upper two thirds of the film, but the pelvis appeared clear. A gastrointestinal series showed a normal esophagus. The antrum of the stomach was displaced upward at the start of the examination,

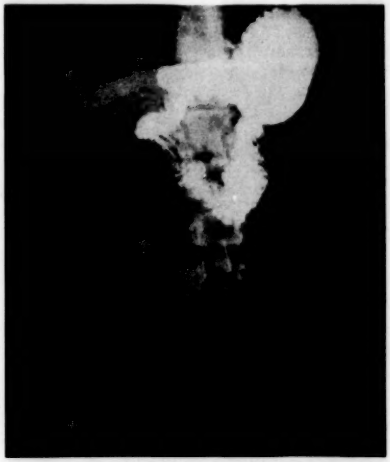

FIGURE 1. *Barium-Meal Examination.*
Note the high position of the stomach and the pressure deformity on the lateral aspect of the second portion of the duodenum.

and the duodenal loop displaced toward the left (Fig. 1). Later on in the examination, however, the distended antrum of the stomach could be made to assume a more normal position, and with the patient in the erect posture, the duodenal loop demonstrated less displacement. The spleen and liver did not appear enlarged. The outlines of the kidneys were not well visualized. Serial films of the barium column showed the small bowel to be entirely on the left side of the abdomen except for the distal ileum which crossed the midline and showed some evidence of extrinsic pressure upon it (Fig. 2). A barium-enema examination showed that the barium readily entered the rectum to reach the cecum without delay. The cecal cap was not completely filled, but this was thought to be mechanical rather than organic. The bowel did not appear particularly displaced, except possibly in the region of the transverse colon, where it may have been displaced somewhat cephalad (Fig. 3). No unusual

defects in bowel outline were noted. Films taken after evacuation disclosed moderately good emptying.

On the ninth hospital day an operation was performed.

Presentation of Case

Dr. Edward Hamlin, Jr.*: This is a rather bizarre history. The x-ray interpretation, the presence of tympany and the absence of shifting dullness all rule rather against ascites. I think it is

Figure 2. *Small-Bowel Examination.*
Marked displacement of the small-bowel loops to the left is apparent. The lower horizontal loops represent the terminal ileum.

fair to assume that this patient had a cyst in the upper abdomen, probably more on the right side than on the left. It also seems fair to assume that the cyst contained rather bland fluid because the story of probable rupture of a cyst five years before entry, with diuresis of its contents, and without a clear story of peritonitis indicate that no strong ferments or bacteria were present. It seems probable that something had recently happened to the cyst to bring the patient to the hospital, because except for mild constipation and an unwillingness to go swimming, there was no adequate reason for his entry. The most likely happening would be hemorrhage into the cyst which is borne out by the hemorrhagic fluid obtained on abdominal tap, and diaphragmatic irritation from the leakage in the wall of the cyst.

Cysts in the upper part of the abdomen may arise from almost any tissue. There is good reason to rule out the spleen because a splenic cyst should be on the left side of the abdomen and there was x-ray evidence that the spleen was not particularly enlarged. The liver is a possibility although I have never heard of a cyst of the liver of this apparent size. Cysts of the mesentery may occur, and may be very large. They may be of various types. Cysts of the omentum may occur, but one of this size would be unusual. The adrenal seems extremely unlikely to produce anything so large. The kidneys certainly could produce a cyst of this size. I do not know whether or not a cyst of this size could be present with completely normal function of the

Figure 3. *Barium-Enema Examination.*
The cecum is high in position, and the transverse colon is displaced upward.

kidneys and apparently very little displacement of the kidneys. Cysts may arise from the retroperitoneal tissue in a sort of nonspecific manner. My problem is to find out where this cyst arose, and it therefore seems that the anatomy or geography of the abdomen would help me more than anything else. Perhaps Dr. Hanelin can help me.

Dr. Joseph Hanelin: The film of the chest shows only a small amount of fluid at the left base.

*Assistant surgeon, Massachusetts General Hospital.

I think Dr. William R. Eyler, who interpreted most of these examinations, believed from the onset that a cyst was present. Initially, there was serious question whether or not we were dealing with massive ascites, but because of normal density within the bony pelvis Dr. Eyler assumed that the fluid was loculated and contained within a cyst. Visceral outlines are obscured; there is bulging at both flanks. No abnormal distention of the bowel is noted. The barium-enema examination is essentially negative although the transverse portion of the colon is unusually high. There is evidence of extrinsic pressure upon the medial aspect of the cecum (Fig. 3). In the retrograde pyelogram the position of the kidneys is normal. This film demonstrates the mild right hydronephrosis, with evidence of pressure upon the ureter at the brim of the pelvis.

Of particularly great help is the small-bowel examination, which shows quite conclusively that there is a localized collection of fluid causing displacement of the small-bowel loops to the left. Only a small segment of terminal ileum crosses the midline (Fig. 2). With ascites, ordinarily, the small bowel retains a relatively normal position.

Dr. Hamlin: I have seen that in conditions other than abdominal cysts — in various forms of congenital anomalies.

The difficulty here is to determine where the cyst arose. The fact that the duodenal loop is pushed over to the left baffles me somewhat. My first choice was pancreatic cyst, which certainly fulfills most of the conditions. It is difficult to postulate a pancreatic cyst that would displace the duodenum to the left. A pancreatic cyst may take various pathways in its gradual protrusion through the abdomen; it may easily displace the stomach and the transverse colon upward and may also push the transverse mesocolon upward and cephalad, but it is very difficult for me to understand how it could possibly push the duodenum to the left.

Dr. Hanelin: There was no anterior displacement of the loop.

Dr. Hamlin: I was hoping that by some chance enough anterior displacement of the duodenal loop had been present to allow for that. I think that is a lost cause. Mesenteric cysts, in my opinion, come under the same difficulties because no matter where the root of the mesenteric cyst arises, it would be very unlikely to displace the duodenum to the left. An omental cyst possibly could. A cyst of the liver certainly could, although a liver cyst of this size is something that I have not run across either clinically or in reading.

The lack of symptomatology is extraordinary and I believe reflects merely the chronicity of the cyst in that the boy grew up with it and therefore it was an old friend and did not bother him very much. Perhaps one of the more pertinent reasons for shifting from the idea of a pancreatic cyst about which I am prepared to say quite a lot to cysts of other natures is the appearance in the front row of Dr. Colby,* who I cannot believe would be here for other than malicious business. I do not know very much about cysts of the kidneys of this nature, but I should suppose that a cyst appearing on the anterior surface of the kidney could enlarge in this manner without causing anterior displacement. I am falling back on the fact that the kidney is about the only structure left that will fulfill the geographic placement of this cyst, its chronicity and other matters. It is certainly more likely that the diuresis following this fascinating rupture of the cyst would be through a kidney cyst than through a pancreatic cyst. That anyone in a period of a few hours could pick up that amount of fluid loose in the abdomen and have diuresis so rapidly seems very unlikely. I shall have to fall back on a cyst of the kidney with recent hemorrhage into it to cause its enlargement.

Dr. Hanelin: The kidney outline can be seen and looks quite normal.

Dr. Allen G. Brailey: Did you consider the possibility that the cyst ruptured directly into the urinary tract?

Dr. Hamlin: I think that is possible.

Dr. Fletcher H. Colby: I am quite certain about one thing: that a cyst so large that arose from the kidney would result in a deformity of the renal pelvis. I cannot believe that the mass had any relation to the kidney. A rupture into the renal pelvis could occur with a simple cyst of the kidney, and sometimes they actually communicate with the excretory pathway and urine is in the cyst itself. That is most unusual, but there frequently is such a very thin membrane between the renal pelvis and cyst that one could easily imagine that trauma might result in a sufficient amount of increased pressure in the cyst to drain out into the renal pelvis. I cannot explain why the patient lost "4 quarts" of urine in such a short time.

*Chief, Urology Service, Massachusetts General Hospital.

DR. HAMLIN: I do not believe we should hold to that too much. That is simply a story. The difficulty to me is to explain the position of the cyst.

DR. COLBY: Can cysts of this nature arise from retroperitoneal structures other than the kidney?

DR. HAMLIN: Yes; a simple cyst representing an embryonic rest can arise practically anywhere. Such a cyst could have been present, but that is such a broad field that I did not want to go into it.

CLINICAL DIAGNOSIS

Mesenteric cyst.

DR. HAMLIN'S DIAGNOSIS

Cyst of kidney, with hemorrhage into cyst.

ANATOMICAL DIAGNOSIS

Congenital solitary cyst of liver.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Dr. Benson B. Roe operated on this patient with a preoperative diagnosis of mesenteric cyst. He found that most of the abdominal cavity was occupied by a cystic mass, which had a few filmy adhesions to the omentum but was really only attached to the liver superiorly. During manipulation of the mass in an attempt to deliver it, it was perforated and was found to contain chocolate-colored fluid, about 2500 cc. of which was aspirated. After delivery of the cyst, the abdominal organs were found to be essentially normal. Both kidneys, the spleen, the stomach and the small and the large bowel were markedly displaced but not involved. The cyst had a broad base, which was confluent with the anterior edge of the right lobe of liver, whence it obviously arose. Its medial wall lay at the gall bladder, which did not connect with it but was displaced about 5 cm. by the cyst. On microscopical examination, it was lined with cells that could be taken to be bile-duct epithelium. The wall of the cyst was very fibrous, trabeculated and fused with normal liver parenchyma. Carcinoma has been reported occasionally to have developed in some of these congenital cysts of the liver, but there was no evidence of malignant degeneration here. I do not know how to explain the episode of diuresis. It seems almost inconceivable to me that the patient could have produced "4 quarts" in such a short period. I understand that he was questioned by about a dozen people, and he stuck to the story.

DR. HANELIN: How about a rupture of a cyst into the peritoneal cavity and absorption from the free peritoneal space?

DR. HAMLIN: That is the only way it could have happened, but there is nothing that I am aware of that will be absorbed at that rate. Is the size of this for a liver cyst unusual? I looked up liver cysts and found nothing that would even approach this.

DR. CASTLEMAN: It was the largest one that I have ever seen.

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BALM OF GILEAD

THE mortality experience of the Metropolitan Life Insurance Company for the first nine months of 1950 reveals a record low death rate of 6.4 per 1000 policyholders. Although the principal communicable diseases of childhood are being virtually eliminated as causes of death, the toll attributable to degenerative disease shows no such decline. Meanwhile, death rates from cancer, diabetes and motor vehicle and occupational accidents actually mount.

Vitamins, immunizations, antibiotics and skillful surgery help to make man live longer, but the environmental obstacles that plague the race have a way of posing as many new problems as were just solved. The biologic seesaw keeps coming down no matter how frantically man props and shores the end that is up.

When people do not die young, they live to die at older ages. A 20,000,000 rise in the population of the United States occurring in the past ten years means that the chronic problems of overcrowding, aging, unemployment and lack of housing or food are replacing the acute outbreaks of yesteryear — the great plagues of smallpox, yellow fever and cholera. When the international scene is considered, war is revealed as another great epidemic disease that takes its toll just as surely as accidents due to motor vehicles and occupational hazards. The scientist and the physician have little cause for complacency despite their impressive charts, which show only one part of the broad picture.

The advances of three thousand years of civilized living have been great, and yet man's progress as a rational animal engaged in the experiment of social living seems spotty and disproportionately slow. Still to be heard rising above the din of twenty million radios proclaiming the merits of Alka-Seltzer, antihistamines and aspirin, is Jeremiah's lament, "Is there no balm in Gilead; is there no physician there?"

A CENTURY OF OPHTHALMOSCOPY

THE year 1950 marked the hundredth anniversary of one of the truly great discoveries in the history of medicine and certainly the greatest in the history of ophthalmology. For it was in 1850 that Helmholtz devised a method of visualizing the hitherto dark recess of the fundus oculi. An entirely new world was opened by this discovery, of momentous significance to medicine in general and to ophthalmology in particular. Indeed, it made a science of ophthalmology the history of which, as Shastid has stated, consists of two eras, the one preceding and the other following the discovery of the ophthalmoscope. In his immortal monograph, *Beschreibung eines Augenspiels*, published in Berlin in 1851, Helmholtz gave a clear description of his new instrument, and it is surprising that this work was never translated into any other language until 1918, when Shastid rendered the English translation.

The influence of this instrument on medicine is incalculable, and without it ophthalmology could

hardly be classed as a science. In the field of diagnostic instruments, few have proved more valuable than the ophthalmoscope. The prophetic vision of Helmholtz regarding its value is attested by the following statement from the original publication: "In brief, I believe that I may hold the expectation not to be exaggerated, that all the alterations of the vitreous body and of the retina which, until now have been found in cadavers, will also permit of recognition in the living eye — a possibility which appears to promise the most remarkable advances for the hitherto undeveloped pathology of this structure." Proof of this prophecy was not long in coming, numerous reports appearing in the years that immediately followed describing the appearance of the ocular fundus in various pathologic states.

Although Helmholtz is rightfully honored with the discovery, it is of interest that in 1847 Charles Babbage, an English mathematician, showed Wharton Jones, the leading London clinician of his day, a model of an ophthalmoscope based on the same principles as that presented four years later by Helmholtz. To his discredit, Wharton Jones apparently failed to grasp its significance, and it was not until 1854 that Babbage's work was revealed. Shades of Long and Morton!

Hermann von Helmholtz was truly a man of genius, and the world of science as well as that of medicine is indebted to him. His masterly paper on the conservation of energy was instrumental in the general acceptance of this doctrine. He made fundamental contributions in neurophysiology, and his study of the sensations of sound is a milestone in the development of the science of acoustics. Physiologic optics had a special attraction for him, and his work in this field is still classic.

The ophthalmoscope has enjoyed a hundred glorious years. Proficiency in the use of the instrument is mainly contingent on the student's becoming familiar with it by repeated use. The diligent and persevering student or physician will find his efforts richly rewarded not only by the acquired ease of use but also by the positive information obtained thereby in many varied disease states. Dilatation of the pupil is sometimes desirable and on occasions quite necessary for satisfactory ophthalmoscopy. However, the experienced observer will find routine examination of the eye grounds, particularly the area of the optic disk, in no way difficult. If all, therefore, would make the effort to become better acquainted with this ingenious instrument, its history in the next hundred years might be even more glorious.

THE LAW RELATING TO ADOPTION

PARENTHOOD, the nearly inescapable result of an almost universal biologic urge, frequently entered into with practically no thought of its future responsibilities, is nevertheless a serious business.

The occurrence of natural parenthood as a by-product of marriage is not only subject to few legal restrictions in any known society, but its restriction under some forms of government is actually discouraged by law.

Parenthood by adoption, on the other hand, possible only as the result of a statutory provision, can be controlled and safeguarded, and increased efforts are rightly being made to protect those future citizens who may become its beneficiaries — or its victims.

An act to make certain revisions in the laws relating to adoption of children, passed by the General Court of Massachusetts in August, 1950, is an example of legislation to this effect. According to this act a decree for adoption shall not be made without the written consent of a child, if over twelve years of age, of the husband if the subject is a married woman, of the lawful parents or the surviving parent and of the mother if the child is illegitimate.

The interest that the state thus takes in adoption is specific, for

> Upon the filing of a petition for adoption of a child under the age of fourteen, notice shall be given to the department of public welfare which shall make appropriate inquiry to determine the condition and antecedents of the child for the purpose of ascertaining whether he is a proper subject for adoption, and to determine whether the petitioners and their home are suitable for the proper rearing of the child, due regard being given the race and religion of the child and of the petitioners.

Exempted from this provision are only charitable corporations organized under general or special laws "for the purpose of engaging in the care of

children and principally so engaged," which corporations shall make written reports accompanying the petitions having the same force and effect as a report of the Department of Public Welfare.

The law contains the usual assortment of teeth, for others who in any way offer for adoption or hold themselves out as being able to dispose of children in any manner shall be punished by a fine of not less than $10 nor more than $100, and those who accept payment in return for placing a child for adoption shall be punished by a fine of $100 to $1,000 or by imprisonment for not more than a year, or both.

In this way the traffic in babies, which at times and in places has assumed such disgraceful proportions, shall be prevented from having a place in the Commonwealth. As with all laws, the wisdom and honesty with which this one is enforced will depend on the wisdom and honesty of those who are selected to enforce it.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

THE time-honored *American Journal of the Medical Sciences* has undergone a recent change in editorship. This periodical, which first appeared in Philadelphia in 1804 as the *Medical Museum*, represents the oldest medical journal in the United States that is still being published, after a lapse from 1813 to 1820. Its present title was assumed in 1827.

For a quarter of a century the journal has been identified with the distinguished editorship of Dr. E. B. Krumbhaar, who has recently laid down this exacting although rewarding task. Beginning with the issue of January, 1951, it will be under the editorial direction of Dr. Richard A. Kern, professor and head of the Department of Medicine of Temple University School of Medicine in Philadelphia.

Dr. Kern will be assisted by a new associate editor, Dr. Thomas M. Durant, professor of clinical medicine, and an assistant editor, Dr. Chris J. D. Zarafonetis, associate professor of internal medicine at Temple University.

It appears that from these woods and Templed hills the voice of scientific freedom shall still ring!

The editor of the New York Medical Gazette upholds the medical faculty of Harvard University, in admitting to the lectures colored students intended for the Colony in Siberia.

Boston M. & S. J., *January 8, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BARONE — Joseph Barone, M.D., of Boston, died on December 26. He was in his sixty-fifth year.

Dr. Barone received his degree from Tufts College Medical School in 1911. He was director of the Bellevue Hospital in Brookline and was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow, three daughters, a son, two sisters and three brothers survive.

BRAGG — Leslie R. Bragg, M.D., of Webster, died on December 11. He was in his seventy-eighth year.

Dr. Bragg received his degree from Harvard Medical School in 1901. He was a member of the New England Roentgen Ray Society and a fellow of the American Medical Association.

A brother survives.

CAVANAUGH — Thomas E. Cavanaugh, M.D., of Springfield, died on December 22. He was in his seventy-sixth year.

Dr. Cavanaugh received his degree from Georgetown University School of Medicine in 1900.

His widow, a daughter, a son, five grandchildren, a sister and a brother survive.

HAPGOOD — Lyman S. Hapgood, M.D., of Cambridge, died on December 28. He was in his seventy-seventh year.

Dr. Hapgood received his degree from Harvard Medical School in 1901. He was a fellow of the American Medical Association.

His widow and a son survive.

MISCELLANY

NATIONAL JEWISH HOSPITAL

Dr. Harry J. Corper, who for the past thirty years has been director of research at the National Jewish Hospital in Denver, Colorado, will shortly retire. The Department of Research, during its thirty years, has published many original investigations in the field of tuberculosis. During this period, the Research Department received numerous scientific awards including the award from the Committee on Scientific Research of the American Medical Association, the Trudeau Medal of the National Tuberculosis Association, the Burdick Medal of the American Association of Clinical Pathologists and the Koher Medal of the American Association of Physicians. In recognition of the position that has been attained the Board of Directors of the National Jewish Hospital propose to increase the budget and enlarge the facilities devoted to research. The Board of Directors is seeking a qualified young man for the position of director. Plans are being developed by the Board for recognition of Dr. Corper's outstanding services.

BOOK REVIEW

Clinical Pathology: Application and interpretation. By Benjamin B. Wells, M.D., Ph.D. 8°, cloth, 397 pp., with 32 illustrations. Philadelphia: W. B. Saunders Company, 1950. $6.00.

Clinical pathology has reached its full maturity in this century and is of great diagnostic help to the clinician. In some cases, however, it is being overdone at the expense of the clinical examination, which is still of prime importance. A clinician, in selecting the right tests in each case, finds that laboratory diagnosis is of value for confirmation or exclusion of a suspected diagnosis, or for the exclusion of unsuspected abnormalities or further investigation of symptoms. From that point of view this book is a great aid in helping the physician to interpret laboratory findings.

The volume starts with a chapter on infectious diseases, gastrointestinal symptoms, diseases of the respiratory system and genitourinary tract, diseases of the blood and cardiovascular system and metabolic and endocrine disturbances. It also has a chapter on clinical laboratory studies in surgery and in obstetrics, and a final chapter on laboratory aids in symptom diagnosis that should be read by every physician who wishes to appreciate the right place of clinical pathology. This book should be valuable to every practitioner of medicine.

NOTICES

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, January 16, at 12 noon. Dr. Conrad Wesselhoeft, professor of clinical medicine, Boston University School of Medicine, will speak on the subject "Recent Advances in Virus Disease."

All physicians are cordially invited to attend.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Wednesday, January 17, at 8:15 p.m. The meeting will consist of a symposium on "Blood Disorders." Dr. Maurice B. Strauss will act as chairman, and the speakers will be Dr. William B. Castle, Dr. Joseph Ross, Dr. Benjamin Alexander and Dr. Max Wintrobe, of Salt Lake General Hospital, Salt Lake City, Utah.

HAMPDEN DISTRICT MEDICAL SOCIETY

A meeting of Hampden District Medical Society will be held at the Hotel Kimball, Springfield, on Tuesday, January 23, at 6:30 p.m. Dr. Leland S. McKittrick, president of the Massachusetts Medical Society, will be the speaker. Members of the Woman's Auxiliary will be guests.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association will present the following lecture in the evening lecture series Thursday, January 25, at 7 p.m. in the Dowling Amphitheater of the hospital.

Surgical Treatment of Involuntary Movements. Dr. A. Earle Walker, professor of neurosurgery, Johns Hopkins University School of Medicine.

All interested persons are invited at attend.

COLLEGE OF MEDICAL EVANGELISTS

The annual postgraduate convention of the College of Medical Evangelists School of Medicine will be held at the Biltmore Hotel, Los Angeles, March 11 to 16. Many eminent medical speakers will present practical and comprehensive syntheses of latest advances in medicine that can be put to immediate use. This program has been planned by a committee consisting of both general practitioners and medical-school faculty.

HYMAN MORRISON LECTURE

On Thursday evening, March 22, in the Dowling Amphitheater of the Boston City Hospital, Dr. Charles K. Friedberg, of Columbia University College of Physicians and Surgeons, will deliver the annual Hyman Morrison Lecture sponsored by the two undergraduate medical chapters of Phi Lambda Kappa Fraternity at Tufts College Medical School and Boston University School of Medicine, respectively. The subject of the lecture will be "Electrolytes in Congestive Heart Failure." All interested persons are cordially invited to attend.

AMERICAN COLLEGE OF ALLERGISTS

The seventh annual meeting of the American College of Allergists will be held at the Edgewater Beach Hotel, Chicago, on February 12, 13 and 14. The program will consist of the following section meetings: "Psychosomatic Aspects of Allergic Diseases (under the leadership of Harold Abramson, M.D., of New York City); "Pediatrics" (under Bret Ratner, M.D., of New York City); "Allergies of the Nose and Throat" (under George Shambaugh, M.D., of Chicago); "Allergic Diseases of the Skin" (under Rudolph Baer, M.D., of New York City); and "Allergic Aspects of Rheumatism and Arthritis" (under George Rockwell, M.D., of Cincinnati). At the general session of the College hay fever, asthma and the newer drugs will be discussed under the leadership of John Mitchell, M.D., of Columbus, Ohio, president of the College.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 15. New England Cardiovascular Society. Page 37, issue of January 4.

JANUARY 16. South End Medical Club. Notice above.

JANUARY 17. Greater Boston Medical Society. Notice above.

JANUARY 17. Boston City Hospital House Officers' Association. Page 1066, issue of December 28.

JANUARY 17. New England Pediatric Society. Page 1066, issue of December 28.

JANUARY 19 AND 20. National Research Council, Committee on Human Reproduction. Page 1066, issue of December 28.

JANUARY 22. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

JANUARY 23. Norfolk District Medical Society. Page 629, issue of October 19.

JANUARY 23. Hampden District Medical Society. Notice above.

JANUARY 25. Boston City Hospital House Officers' Association. Notice above.

JANUARY 29. Suffolk District Medical Society. Page 37, issue of January 4.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

FEBRUARY 8. Leukemia. Dr. Joseph Ross. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

FEBRUARY 9. Beta Iota Chapter of Nu Sigma Nu. Page 1018, issue of December 21.

FEBRUARY 11. National Conference on Medical Services. Page 38, issue of January 4.

FEBRUARY 12–14. American College of Allergists. Notice above.

FEBRUARY 13. New England Society of Anesthesiologists. Page 512, issue of September 28.

FEBRUARY 21. Bay State Society for the Crippled and Handicapped. Page 1066, issue of December 28.

FEBRUARY 27. Norfolk District Medical Society. Page 629, issue of October 19.

MARCH 11–16. College of Medical Evangelists. Notice above.

MARCH 22. Hyman Morrison Lecture. Notice above.

DISTRICT MEDICAL SOCIETIES

HAMPDEN

JANUARY 23. 6:30 p.m. Hotel Kimball, Springfield.

NORFOLK

JANUARY 23. 8:00 p.m. Boston Medical Library, 8 Fenway, Boston.

SUFFOLK

JANUARY 29. 8:30 p.m. Chelsea Naval Hospital.

(*Notices concluded on page xix*)